EARLY DETECTION OF LUNG INVOLVEMENT IN RHEUMATOID ARTHRITIS PATIENTS

Dissertation submitted to
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
In partial fulfilment of the Regulations
for the award of the degree of

(M.D. PHYSIOLOGY)
BRANCH-V

THANJAVUR MEDICAL COLLEGE , THANJAVUR

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERISTY

CHENNAI, INDIA

MAY – 2018

CERTIFICATE

This dissertation entitled **"EARLY DETECTION OF LUNG INVOLVEMENT IN RHEUMATOID ARTHRITIS PATIENTS"** is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the regulations for the award of M.D., Degree in physiology in the Examinations to be held during May 2018.

This Dissertation is a record of fresh work done by the candidate Dr.S.JEYAKUMAR, during the course of the study (2015-2018). This work was carried out by the candidate himself under my supervision.

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DECLARATION

I solemnly declare that the Dissertation titled **"EARLY DETECTION OF LUNG INVOLVEMENT IN RHEUMATOID ARTHRITIS PATIENTS"** is done by me at Thanjavur Medical College, Thanjavur

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Approval No. : 249

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.....EARLY DETECTION OF LUNG INVOLVEMENT IN.....

.....RHEUMATOID ARTHRITIS.....

submitted by Dr. .....S. JEYAKUMAR..... **of**

Dept. of .....PHYSIOLOGY..... **Thanjavur Medical College, Thanjavur**

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Thanjavur

Dated : .....26.2.16.....

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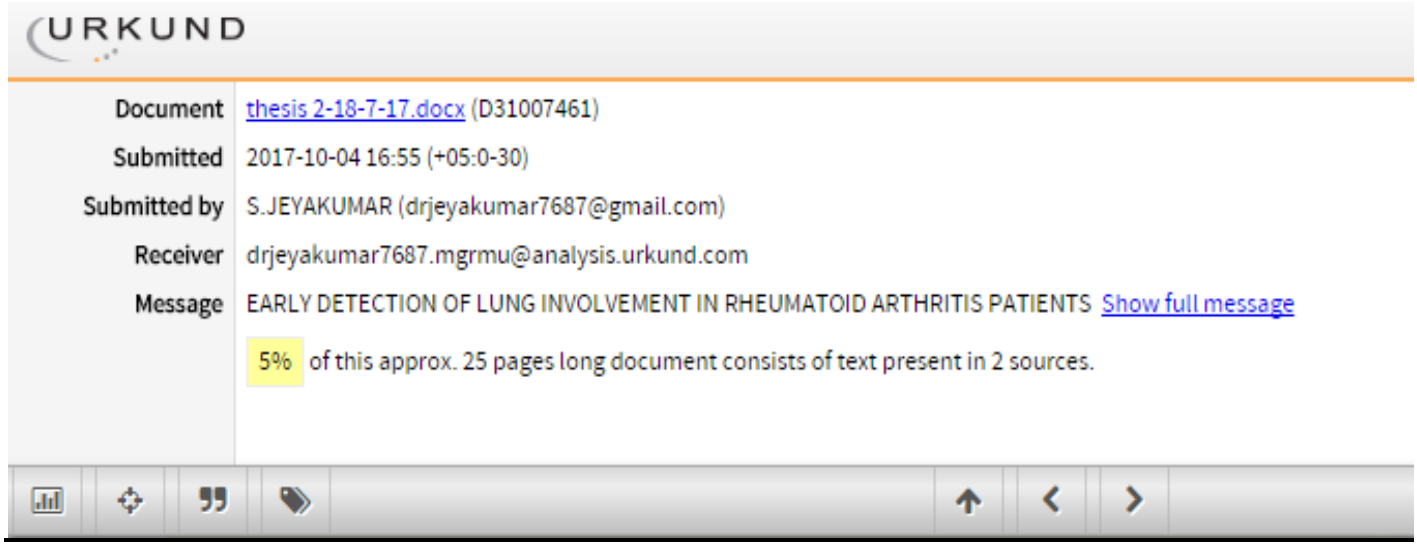

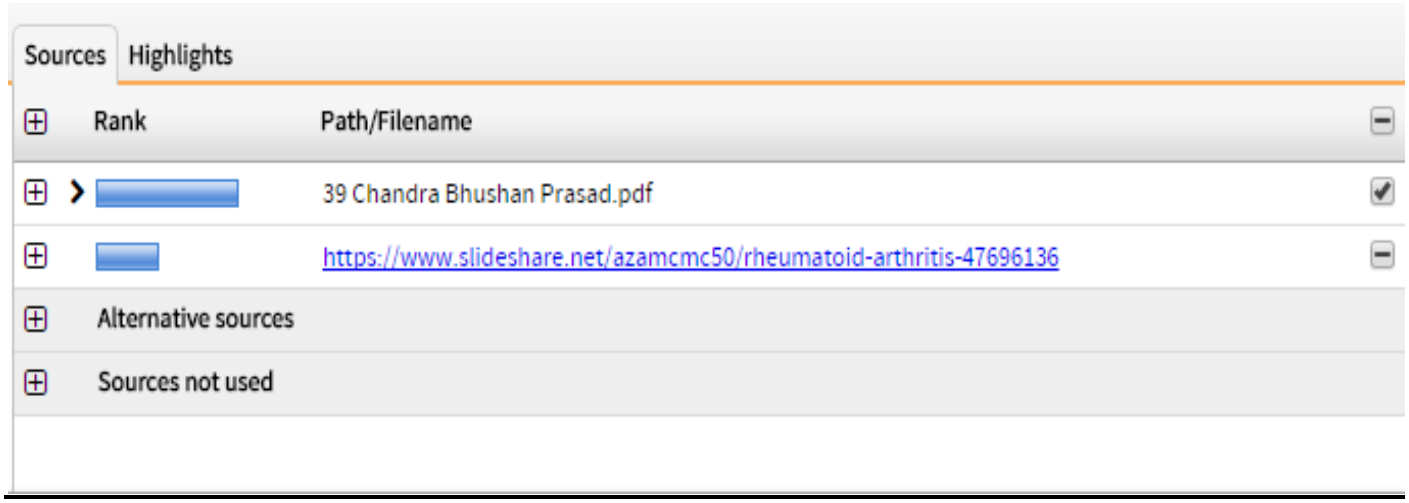

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This is to certify that this dissertation work titled **"EARLY DETECTION OF LUNG INVOLVEMENT IN RHEUMATOID ARTHRITIS PATIENTS"** of the candidate **Dr.R.AKILA** with registration Number **201515203** for the award of **M.D.,** in the branch of **PATHOLOGY** I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **7** percentage of plagiarism in the dissertation

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ABSTRACT

TOPIC: EARLY DETECTION OF LUNG INVOLVEMENT IN RHEUMATOID ARTHRITIS PATIENTS

AIM:

The Aim of the study was to assess the early involvement of lung in Rheumatoid Arthritis patients.

METHODS AND MATERIALS:

For this study, 40 normal control group in the age group between 25-55 years and 40 patients with Rheumatoid Arthritis of <5 yrs duration as study group were selected as per American Association Criteria of Rheumatology. This Study was conducted at Research Laboratory, Department of Physiology, Thanjavur Medical College, Thanjavur. The Study group was from the Thanjavur Medical College & Hospital, Thanjavur.

Patients with Diabetes Mellitus, Alcoholism, Neuropathy, Chronic Tuberculosis, Carcinoma lung, Metabolic disorders and other connective tissue disorders were excluded. Informed written consent were obtained from the patients of Thanjavur Medical College & Hospital.Ethical committee approval obtained before starting the study.

In this study, FVC, $FEV_{1,}$ FEV_{1}/FVC, MVV and PEFR were compared and statistically analyzed.

RESULTS :

The results showed statistically significantly reduced pulmonary function parameters FEV_1, FVC, MVV & PEFR ($P<0.05$). However FEV_1/FVC (%) was mildly increased which was not statistically significant in Rheumatoid arthritis patients.

CONCLUSION:

The result of the present study shows that there is a decrease in pulmonary function in Rheumatoid arthritis patients when compared with healthy controls.

Key Words: Rheumatoid arthritis with Lung involvement, Pulmonary function tests, RA factor and CRP.

INTRODUCTION

Rheumatoid arthritis is a chronic systemic inflammatory disease which affects multiple joints; leading to progressive, symmetric, erosive cartilage &bone destruction. Rheumatoid arthritis is commonly associated with elevated auto antibodies. (1)

Rheumatoid arthritis affects 0.3-2.1% of population in worldwide with the age group of 25-55years (2). It is more common in females than in males. It is 2-4 times more common in first degree relatives (3).

RA is 2-3 times more common in women, but the sex ratio is different depending on age at onset. In individuals 20-30 years of age, the incidence is much higher in women, whereas rates are higher in men aged > 50 and closer to those seen in postmenopausal women .The median age of onset is 55-60 years, but RA can occur at any age. The incidence appears to be rising with increasing age up to the age of 80(4).

Metacorpophalangeal (MCP)joints, Interphalangeal (IP) joints of thumb, Proximal interphalangeal (PIP) joints of fingers, wrists, Metatarsophalangeal (MTP) joints are commonly affected in the early diseases which is followed by involvement of larger joints like elbow joint, shoulder joint, knee & ankle joints.(2,3)

Lung involvement is a common extra-articular manifestation of RA conferring significant morbidity and mortality. It is seen in 30% of the cases. Lung disease is the second most common cause of death following infection

(5).

Extra articular manifestations of rheumatoid arthritis are subcutaneous nodule, vasculitis ,eye involvements and lung disease. The lung manifestations of Rheumatoid arthritis are Interstitial lung disease, pleural effusion, pulmonary hypertension and small airway involvement.(1)

In clinical practice pulmonary function testing is used most commonly to estimate prognosis, follow the course of the disease or the response to therapy, to detect untoward reaction to drugs, and to assess functional impairment or disability.(6)

In our study pulmonary function tests like Forced vital capacity(FVC), forced expiratory volume in 1 second(FEV1),FEV1/FVC Ratio, Slow vital capacity(SVC) and Maximal voluntary ventilation (MVV) were measured to be assess the early involvement of lung in Rheumatoid arthritis patients.

AIMS AND OBJECTIVE

AIM :

The aim of the study was to evaluate the early involvement of lung in Rheumatoid arthritis patients.

OBJECTIVES :

The main purpose of this study was to

1. Study lung function in Rheumatoid arthritis patients.

2. Detect the early involvement of lung in Rheumatoid arthritis.

3. Find out whether it is Obstructive or Restrictive.

REVIEW OF LITRATURE

RHEUMATOID ARTHRITIS:

HISTORY:

The British nomenculature in 1922 and in the USA in 1941 acknowledged the term Rheumatoid arthritis officially.

In England in 1859 Sir Alfred Baring Garrod,1819-1907 coined the term Rheumatoid arthritis.

RA is largely circumstensive by the deformity implied in the classification criteria published in 1958 and reviewed in 1987[7].

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic systemic inflammatory polyarthritis that primarily affects small diarthrodial joints of the hands and feet in a symmetrical pattern. It is a heterogenous disease with variable severity, unpredictable course, and a variable response to drug treatment.[2]

EPIDEMIOLOGY:

The disease prevalence worldwide is approximately 0.8% (0.3%to 2.1%) of the population. In India, the prevalence of RA is 0.5% to 0.75%. The peak age of onset is in the fourth and fifth decade of life with more than 75% patients developing disease between 30 and 50 years of age [2].

RA has an annual incidence of approximately 0.2 per 1000 in males and 0.4 per 1000 in females [7].

AETIOLOGY:

Rheumatoid arthritis (RA) is an autoimmune disease of un kown cause. Genetic and environmental factors play a major role in susceptible persons to develop the disease.

1) GENETIC FACTORS:

RA is commonly seen 2 to 4 times more in first degree relatives. The disease occurs in monozygotic twins approximately 30% to 50%.

The most important genetic susceptibility locus associated with RA is class II Major histocmpatability complex (MHC) alleles of man HLA- DRB1.The group of alleles collectively identified as Shared Epitope(SE).e.g;HLA-DR4(DRβ1*0401).

Amongst Indians RA is highest risk with DRβ1*0405 followed by DRβ1*0401 and DR4 haplotypes on DQβ1*0302 region. Some HLA- DR alleles like DRβ1*1502 and DRβ1*0403 are protective against RA [2].

2) ENVIRONMENTAL FACTORS:

Smoking and infections play a main role in RA.

Tobacco smoking cause repetitive damage to the mucosa of the airways. They will produce constant low grade inflammation. They activate innate immune system by toll like receptors [(2)].

Infectious agents like Epstein-Barr virus (EBV), parvovirus B19, Mycobacterium tuberculosis, Escherichia coli and Proteus mirabilis. These viral and bacterial organisms activate the factors for RA. [(8,9,10,11,12,13)]

Environmental factors indirectly induce factors of RA along with genetic factors.

Some viruses and bacterial agents contain identical peptide sequence to auto antigen. These microbial agents produce immune response that cross react with auto antigen is called " antigen mimicry" [(14)].

Hormonal factors play a major part in females. The high incidence of disease occur during premenopausal or postpartum period. Oral contraceptive pills consumption protect from the disease due to progesterone content. [(15)]

Diet,reduction in Vitamin C intake, large amount of red meat intake and stress also to play a potential role in the disease expression .There is an inverse relationship between RA and Vitamin D which has Immunomodulatory effects. [16,17,18,19,20,21]

TABLE-1

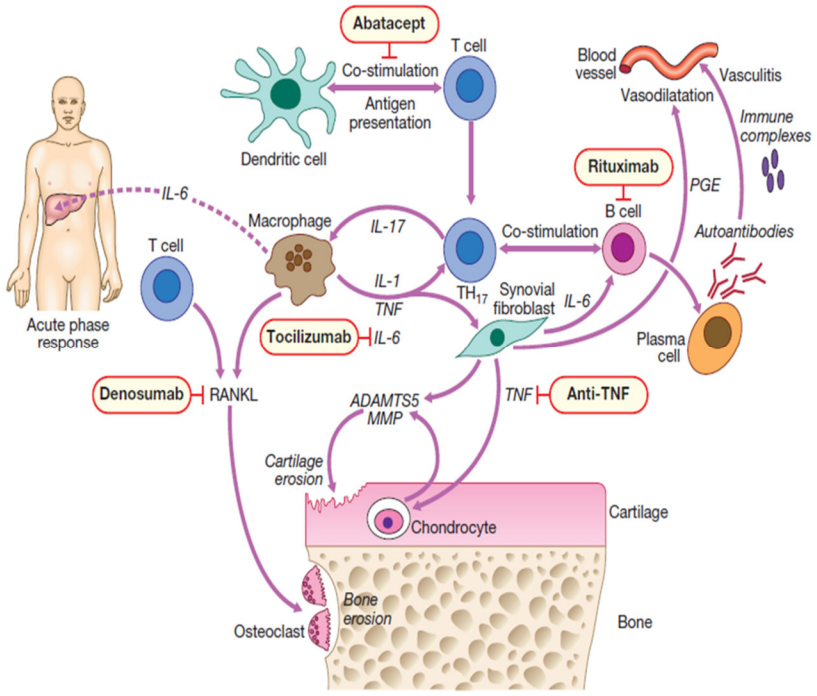
1987 Revised ARA Classification Criteria for RHEUMATOID ARTHRITIS:

	Criterion	Definition
1	Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2	Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3	Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP,or PIP joint
4	Symmetrical arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5	Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta articular regions, observed by a physician.
6	Rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control Subjects
7	Radiographic changes	Radiographic changes typical of Rheumatoid arthritis on postero anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

PATHOGENESIS:

FIGURE-1

This figure shows pathogenesis of Rheumatoid Arthritis:



Genetic, epigenetic and environmental factors are involved in the pathogenesis of RA. The genetic incidence rate of RA is higher in monozygotic twins (12%-15%) than in dizygotic twins(3%).There is incidence of disease frequency is an increased in first degree relatives of patients.[3] The risk genes are involved in immune system are included in Major histocomptablity complex class II, PTPN22,CD40L and CTLA4.The MHC class II gene,HLA-DR4 is most commonly involved in haplotype in ethnic groups seen in 50%-75% Caucasian patients with RA

is compared to 20%- 25% of the normal persons. The DR1 is most common in Indians, Israelis' and DW15 in Japanese.

The pathogenesis of RA is inflammation of the synovial membrane with Lymphocytes, Plasma cells, Dendrites cells and macrophages.CD4 Lymphocytes in the Th1 cells(IFN-γ) and TH 17 cells (IL-17A,IL-17F and IL-22 producers) play a major role in the synovial membrane.[3]

Lymphoid follicles present in the synovial membrane in which T-cell- B-cell interactions lead B cells to produce cytokines and auto antibodies. Which include rheumatoid factor and ACPA. Synovial macrophage are induced by immune complexes and local damage by toll-like receptors to form pro inflammatory cytokines like TNF,IL-1,IL-6 AND IL-15.These cytokines are act on synovial fibroblasts to induce swelling of the synovial membrane and damage to soft tissue and cartilage.

Fibroblasts are consists of rich in inflammatory cytokines, chemokines, leukotrienes and matrix metalloproteinase that will produce local tissue damage and remodeling.

Activation of osteoclasts by RANKL and chondrocytes by cytokines like as IL-1 and TNF produce destruction of bones and cartilages. The RA joint is hypoxic which produce new blood vessel formation (neoangiogenesis) [3].

The inflamed synovial memmbrane become vascularised with activated endothelial cell associated to leucocytes. The main cytokine in RA joint is TNF which is regulate the inflammatory process and also in systemic effects of RA which includes the acute phase response, anemia of chronic disease, fatigue and reduce cognitive functions.

The inflammatory granulation tissue (pannus) formed under articular cartilage which is progressively eroded and destroyed. Maturation of osteoclast in the synovial joint and adjoined with bone eroded. Later fibrosis or ankylosis and muscles will be atrophy with infiltrated lymphocyte [3].

CLINICAL FEATURES:

The incidence of RA peaks at age between 25-55 years .Then it will be maintained at the same level until the age of 75 years and then declines. The presenting complaints of the RA are due to inflammation of joints , tendon and bursa. RA patients mainly complaint of early morning joint stiffness lasting for more than 1 hour due to physical activity.

The earliest involved joints are small joints of the hands and feet. The type of joint involvement is monoarticular, oligoarticular (<4 joints) or poly articular (>5 joints) with symmetric pattern.[2]

The wrists, metacarpo phalangeal joints and proximal inter phalangeal joints are most frequently involved joints in RA. Distal interphalangeal joints may also involved in RA but it is coexistent with osteoarthritis. Flexor tendon tenosynovitis is a frequent hallmark of RA which will lead to decrease range of motion, reduced grip strength and trigger fingers

[2].

COMPLICATIONS:

Progressive destruction of the joints and soft tissues may lead to chronic ,irreversible deformities. Ulnar deviation results from subluxation of the metacorpophalangeal joints with subluxation of proximal phalanx to the ulnar side of the hand.

"Swan neck deformity"- hyperextension of the proximal interphalangeal joints with flexion of the distal phalangeal joints.

"Boutonniere deformity"- flexion of the proximal inter phalangeal joints with hyperextension of distal inter phalangeal joints.

"Z line deformity"- subluxation of the first metacorpo phalangeal joint with hyperextension of the first interphalangeal joint.(2)

Inflammation of the Ulnar styloid and tenosynovitis of the extensor carpi ulnaris may cause subluxation of the distal ulna produce "piano-key movement" of the ulnar styloid.

In lower limb metatarso phalangeal joint involved in the feet is an early sign of disease.Chronic inflammation of the ankle and involvement of midtarsal joints occur later. This condition is called "pesplano valgus"(flat feet).

Large joints are also involved like shoulder joint and knee joint ,however it is asymptomatic . Atlanto axial joint involvement of the cervical spine also occurred in RA. It will cause compressive myelopathy and neurologic dysfunction.(2)

EXTRA ARTICULAR MANIFESTATION OF ARTHRITIS:

CONSTITUTIONAL:

This disease will produce signs and symptoms of weight loss, fever, fatigue, malaise, depression and cachexia.

SUBCUTANEOUS NODULES:

These nodules occur in 30%-40% of RA patients. It will be present with highest levels of disease activity, related to shared epitope, a positive Rheumatoid factor and radiographic evidence of joint erosions.

When palpated nodules are firm, non tender and adherent to periostium and tendons. These nodules are present in forearm, sacral prominence, Achillis tendon. They may also present in lungs, pleura, pericardium and peritoneum. [22]

EYE:

Eye manifestation in RA is otherwise called as secondary Sjogren's syndrome which is associated with the presence of either keratoconjuctivitis sicca (dry eye) or xerosmia (dry mouth) in around 10% of RA patients.

PULMONARY:

Interstitial lung disease is common in RA patients which presents with symptom of dry cough and progressive shortness of breath. It can be diagnosed by HRCT and pulmonary function test with reduced DL_{CO}. It is treated by immunosuppressive therapy. Pleural disease is also common in RA Patients which may produce chest pain, dyspnea, pleural friction and pleural effusion and is exudative with increased amount of neutrophils and monocytes.[22]

CARDIAC:

The most common cause of death in RA patients is cardiovascular disease. The major site of cardiac involvement is pericardium. Pericarditis occurs in less than 10% of the RA patients. Diagnosed by echocardiogram or autopsy studies. Other cardiac manifestations are Cardiomyopathy, Coronary artery disease and Mitral regurgitation.

VASCULITIS:

Rheumatoid vasculitis is seen in RA patients with long standing disease. Associated with positive rheumatoid factor and hypo complementemia which occurs <1% only. The cutaneous signs are petechiae, purpura, digital infections, gangrene and Livedo reticularis.

HEMATOLOGICAL:

A normochromic, normocytic anemia often develops in RA patients. The degree of anemia with parallel degree of inflammation is correlated with levels of serum CRP and ESR. Platelet also increased due to acute phase reactants. Felty's syndrome is defined as triad of neutropenia , splenomegaly and nodules RA which is present in less than 1% of RA patients. T-cell large granular lymphocyte leukemia(T-LGL) is also associated with RA.

LYMPHOMA:

The studies show 2 to 4 fold increase risk of lymphomas in RA. The most common type is a diffuse large B-cell lymphoma. The lymphoma developing risk will be more is associated with felty's syndrome.

OSTEOPOROSIS:

Osteoporosis in RA patients is more prevalent in 20%-30%, due to bone loss by osteoclast activity. Chronic use of Glucocorticoids also contributes osteoporosis.

HYPO-ANDROGENISM:

Men and postnmenopausal women with RA have lower level of serum testosterone, Leutinising hormone, Dehydro epiandrosterone (DHEA). Hypo androgenism play a role in the pathogenesis of RA. The higher serum testosterone level will produce some protective role in RA.

Hypo androgenesis due to chronic use of glucocorticoids produce inhibition of LH, FSH secretion from pituitary gland. Treated by androgen replacement therapy.[22]

LABORATORY DIAGNOSIS:

Systemic inflammation is diagnosed with ESR (Westergren method) and CRP levels. Albumin synthesis by liver is depressed by systemic inflammation leading hypoalbuminaemia.

In active RA reversal in albumin/globulin ratio is common. Serum alkaline phosphatase (ALP) is increased in active RA.

Liver enzymes, renal parameters, blood glucose and routine urine examination are also done. These are essential since certain drugs used in RA are cleared (NSAIDs, MTX, LEF) by the liver. In compromised renal status (MTX) drug dosages require to be modified.[(2)]

RHEUMATOID FACTORS:

Rheumatoid factors are auto antibodies directed to the Fc portion IgG. This part of the molecule is essential for complement fixation interaction with the Fc receptor and thus for uptake of immune complexes.

RF may be directed to all four IgG subclasses but RF secreted by blood lymphocytes of RA patients appear to be preferentially directed to IgG1andIgG2. IgM-RF is the major RF species but IgG-RF and IgA-RF are also present in serum and synovial of patients with RA.

Measurement of Rheumatoid factors:

- Classic agglutination techniques are most sensitive techniques are most sensitive to IgM-RF because IgM antibodies are more efficient in agglutination reactions.
- The latex fixation test and the bentonite flocculation test use particles coated with aggregated human IgG, while the sheep cell agglutination test.
- The waaler-rose test, is more specific for RF in RA but less sensitive than assays employing human IgG.
- Widely used tests are Nephelometry and ELISA are able to measure RF subtypes.

Binding sites for Rheumatoid factors:

Rheumatoid factors can bind to several distinct regions within the Fc portion. Binding sites include:

- Ga determinants expressed on IgG1, IgG2 and IgG4.
- Gm determinants associated with particular IgG subclasses and restricted to particular animal species.
- Subclass-specific antigens
- Species-specific antigens
- Neoantigens on altered IgG.

Stimuli for Rheumatoid factor production:

- IgM-RF synthesis can be induced by immune complexes and polyclonal B cell activators such as bacterial lipo polysaccharides or Epstein-barr virus.
- RF is produced during bacterial and viral infections, probably in response to immune complexes containing microbial antigens.
- A distinguishing feature of RF in RA is its persistence in many years.

Rheumatoid factors may be encoded both by germline and somatically mutated genes**.**

Rheumatoid factors are diagnostic and prognostic markers.[7]

C-REACTIVE PROTEIN (CRP):

CRP is an acute phase protein which is present in serum of active inflammation.CRP was identified in 1930,which sera was collected from streptococcus pneumonia patients. That organism contained a protein that bind to the "C" polysaccharides of the bacterial cell wall.

This protein circulates as a 114-kD pentamer of non-covalently linked 23-Kd subunits. Plasma C-reactive protein is synthesized by hepatocytes.

CRP recognize and clear the substance like phosphocholine, phospholipids, fibronectin, chromatin and histones which are present in sites of tissue damage and apoptotic cells.

CRP form the bridge between innate and adaptive immunity by activating classical complement pathway.CRP induces inflammatory cytokines, tissue factors and shedding of the IL-6 receptors, which result is a complement dependent increase in tissue damage.

CRP acts as an anti inflammatory substance, gives clearance of non inflammatory apoptotic cells and prevents neutrophil adhesion to the endothelium.

CRP levels increases in acute inflammatory condition rapidly and peaks at 2 to 3 days due to extent of tissue damage. Plasma half life of CRP is 19 hours. Persistent increase is seen in CRP levels in some conditions like acute Rheumatoid arthritis , pulmonary tuberculosis and malignancy.

Lab diagnosis by Immunoassay method and Laser Nephelometry. High sensitive CRP is most accurate test.

Normal level of CRP in plasma is 0.3 mg/dl. Mild elevation - >1mg/dl, moderate elevation- 1-10mg/dl , high elevation- 10-15mg/dl, very high elevation- >15mg/dl.[23]

IMAGING:

Imaging plays an important role in the diagnosis as well as in the assessment of disease progression. Joints in the hands, wrists and feet have smaller bones and thinner cartilage than the larger joints. Therefore, early radiographic changes are better seen in them and are recommended radiographs at the baseline and for the periodic assessment of joint disease in the follow-up. The earliest abnormality is periarticular osteopoenia, which is nonspecific and variable. With uncontrolled disease more characteristic changes of cartilage loss (joint space narrowing) and bony erosions appear by 6 to 12 months and keep accumulating over time. Magnetic resonance imaging (MRI) and ultrasonic joint examination are more sensitive for detecting joint changes including synovial hypertrophy, joint effusion, tendon and ligament disease, erosions and rupture of joint cysts (e.g. Baker's cyst) than routine radiographs. They could be useful in early arthritis when clinical examination and standard radiographs may be unhelpful.[2]

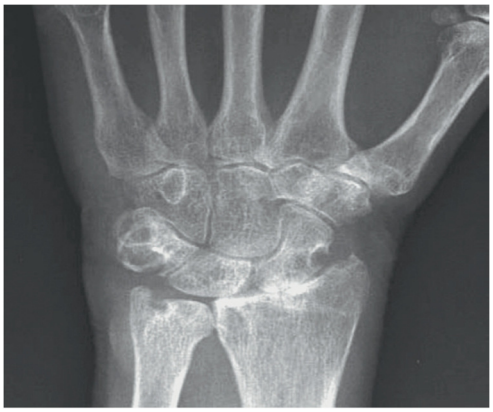


FIGURE-2.RHEUMATOID ARTHRITIS – X-RAY WRIST AND METACORPOPHALANGEAL JOINTS - Bony erosion seen in this figure.

TABLE-2

Modified from the 2010 ACR-EULAR classification criteria for RA:[2]

	SCORE
Target population (Who should be tested?): Patients who 1. have at least 1 joint with definite clinical synovitis (swelling) 2. with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement§ 1 large joint 2-10 large joints 1-3 small joints (with or without involvement of large joints)# 4-10 small joints (with or without involvement of large joints) >10 joints (at least 1 small joint)	 0 1 2 3 5
B. Serology (at least 1 test result is needed for classification) Negative RF and negative ACPA Low-positive RF or low-positive ACPA High-positive RF or high-positive ACPA	 0 2 3
C. Acute-phase reactants (at least 1 test result is needed for classification) Normal CRP and normal ESR Abnormal CRP or abnormal ESR	 0 1
D. Duration of symptoms <6 weeks ≥6 weeks	 0 1

TREATMENT:

Management of Early Rheumatoid Arthritis:[3]

FIGURE-3

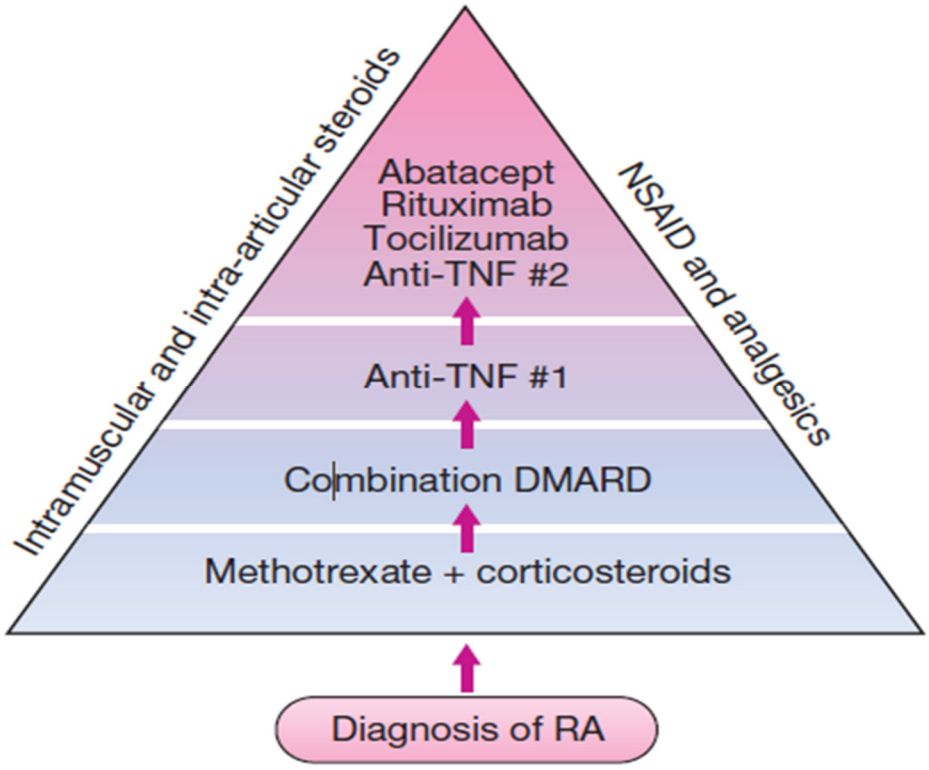


TABLE-3

Commonly used small molecule Disease modifying anti Rheumatoid drugs in Rheumatoid arthritis:

DRUGS	MECHANISM OF ACTION	MAINTANANCE OF USUAL DOSE	PRINCIPLE SIDE-EFFECT	MONITORING REQUIREMENT	MONITORING FREQUENCY
methotrexate	Inhibits DNA synthesis and cell division	5-25 mg /week	GI upset, stomatitis, rash,alopecia, hepatotoxicity, acute pneumonitis.	Full blood count,liver function test	Initially monthly
Sulfasalacine	unknown	2-4g/day	Nausea,GI upset,rash,hepatitis,neutropenia	FBC,LFT	Monthly for 3 months, then 3 monthly
Hydroxychloroquine	unknown	200-400mg/day	Rash,nausea diarrhea,headache,corneal deposit, retinopathy	Visual acuity,fundoscopy	12-monthly
leflunamide	Blocks T-cell division	10-20 mg/day	Nausea,GI upset,rash,hepatitis,alopecia,hypertension	FBC,LFT, BP	2-4 weekly

D-penicillamine	unkown	250-750mg/day	Rash,stomatitis, metallic taste, proteinuria,thrombocytopenia	FBC, Urine for protein	Initially 1-2 weeks,4-6 weeks for main tanance
Gold	unknown	50 mg/week by IM injection	Rash,stomatitis, myelosuppression, proteinuria, thrombocytopenia	FBC, Urine for protein	Each injection
ciclosporin	Blocks T-cell activation	150-300mg/day	Nausea, GI upset, renal impairment, hypertension	FBC,LFT, Urine and Electrolytes	2-4 weekly

TABLE-4

BIOLOGICAL DRUGS USED IN RHEUMATOID ARTHRITIS:

DRUGS	USUAL MAINTANANCE DOSE	COMMENT
ANTI TNF-alpha Etanercept Infliximab Adalimumab Certolizumab Golimumab	 50 mg every week SC 3 mg/kg every 8 week IV 40 mg every 2 weeks SC 200 mg every 2 weeks SC 50 mg every 4 weeks SC	 Decoy receptor for TNF-alpha. Antibodies to TNF,Interferon must be given with methotrexate
ANTI-B-CELL THERAPY Ribuximab	1000 mg IV,Repeat after 2 weeks	Premedication with methylprednisolone 100mg IV,Chlorphenramine 10mg IV and paracetamol given 30 min prior to each injection.
INHIBITOR OF T-CELL Abatacept	125 mg SC once a week	Favourable safety profile
ANTI-IL-6 Toclizumab	8 mg/kg every 4 weeks IV	More effective than anti-TNF in methotrexate – intolerance patients.
ANTI-IL-1 anakinra	100 mg daily SC	Less effective than other biological drugs

RESPIRATORY SYSTEM:

INTRODUCTION:

The primary function of the lung is gas exchange. Which consists of movement of oxygen into the body and removal of carbon dioxide. The lung functioning as host defense by primary barrier between the outside world and inside of the body. Lung also act as a metabolic organ that synthesizes and metabolizes numerous compounds.[24]

The main function of lung is maintenance of the partial pressures of these gases is systemic arterial blood within normal ranges. PaO_2 10.5 - 13.5 kPa (80-100mmHg), $PaCo_2$ 4.8-6.0 kPa(35-45 mmHg).

There are three main compounds to the process of gas exchange. They are Ventilation, Perfusion and Diffusion. [25]

LUNG ANATOMY:

The lungs contain volume of 4L.They have a surface area for gas exchange that is the size of a tennis court-85m^2.This large surface area is composed of myriads of functioning respiratory units.

The division of the lung and site of the disease are anatomically located like right upper lobe, left lower lobe. In adults the lung weight about 1kg, with lung tissue contained for 60% of the weight and blood is occupy the remined area.

Alveolar spaces are most of the lung volume. These spaces are contained tissue is collectively called interstitium. The interstitium is com primarily of lung collagen fibres and is a potential space for fluid and cells to accumulate.

UPPER AIRWAYS:

NOSE,SINUSES, LARYNX:

The respiratory system starts with the nose and ends in the distal alveolus.the nasal cavity, the posterior pharynx, the glottis and the vocal cord, the trachea and cell division of the tracheo bronchial tree are included.

The upper airway consists of all parts from nose to the vocal cords with sinuses and the larynx. The lower airway composed of the trachea and alveoli. The function of the upper airway is to condition inspired air it will maintained body temperature and full humidified. The nose act as a filter and clear the particles larger then 10μ m in size. The nose also provide the sense of smell .In human the volume of air entry through nares 10000 to 15000L per day .[24]

-*LOWER AIRWAYS :

TRACHEA, BRONCHI, BRONCHIOLES, RESPIRATORY UNIT:

The right lung is located in right hemithorax. It consists of three lobes (upper, middle and lower) by two inter lobular fissures (oblique, horizontal).the lung is located in left hemithorax. It consists of two lobes (upper including lingual and lower) by an oblique fissures.

The both lungs are involved are covered by thin membrane is called visceral pleura and then over covered by another membrane is parietal pleura. In between both pleura produce potential space due to expands the chest.

The trachea bifurcates into two main stem bronchi. The main stem bronchi is divide into lobar bronchi. Which in turn divide into lobar bronchi. Which in turn divides into segmental bronchi. Then continuously divide into branches like bronchioles until reaching the alveolus. The segmently bronchus is the functional anatomic unit of the lungs.

The region of the lung supplied by segmental bronchioles is called a broncho pulmonary segment and is the functional anatomic unit of the lung. This structure segments of the lung that have become irreversible disease can early by surgically removed.

The basic physiological unit of the lung is the respiratory or gas exchanging unit is called respiratory unit. Which contained respiratory bronchioles, the alveolar ducts and the alveoli. Bronchi contain cartilage and non respiratory bronchioles (lacking alveoli) is called conducting airways. This area of the lung is greater than 150ml in value does not participate in gas exchange is called anatomic dead space. The alveoli are polygonal in shape and size about 250μ m in diameter. An adult has around 5×108 alveoli. The each alveoli contained type I epithelial cells and type II epithelial cells [24].

Type I epithelial cells occupies 96% to 98% of the surface area of the alveolus .The primary site for gas exchange is thin cytoplasm of type I cells.

Type II epithelial cells is small and cuboidal present in the corners of the alveolus. Which it occupy 2%-4%r of its surface area. Type II cells are synthesis pulmonary surfactant which reduce surface tension in the alveolar fluid. It may also regenerate the alveolar structure due to any injury. Gas exchange occur in the alveoli through a dense mesh like network of capillaries is called alveolar-capillary network. The barrier between gas in the alveoli and the red blood cells is only1to 2 μm in thickness. [24]

INSPIRATION AND EXPIRATION:

Inspiration is an active process. The muscles of inspiration are diaphragm, external intercostals, sternocleido mastoid muscle, serratus anterior and scalene muscle. Their contraction increases the lung volume.

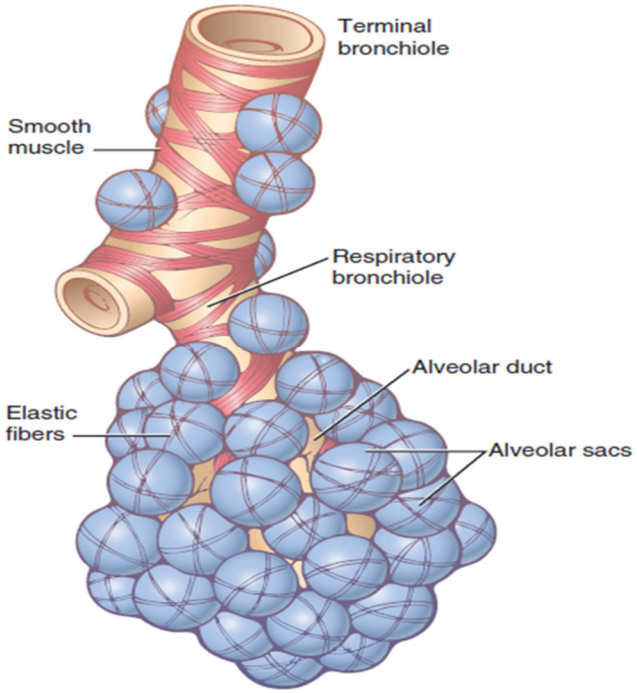
During inspiration the intra pleural pressure become more negative from -2.5 mmHg to -6 mmHg due to expansion of the chest wall. This pulls the surface of lungs with greater force creating negative ntrapulmonary pressure.

At the end of inspiration, the inspiratory muscles relax and the recoiling force of the lungs begins to pull the chest wall back to expiratory position. The pressure in the airway becomes slightly positive and the air flows out of the lungs.

Expiration during quite breathing is passive. At the end –expiratory position where the recoil force of the lungs and recoil force of thoracic cage balance, the pleural pressure returns back to -2.5 mmHg. [26]

LUNG INTERSTITIUM:

FIGURE-4



The lung interstitium or space is consists of connective tissue, smooth muscle, lymphatics, capillaries and a different type of cells. However in diseased conditions the interstitum is enlarged with the influx of inflammatory cells and edema fluid, which can affect with gas exchange in the alveoli.

Fibroblasts are foremost cells in the interstitium of the lung. They synthesis and secrete collagen and elastin. Which are extracellular proteins that participate in matrix formation and in the physiology of lung.

Collagen is most important structural component of the lung .It will limits the lung distensibility.

Elastin is the important contributor to elastic recoil of the lung.

Cartilage is a tough, resilient connective tissue that helps the conductive airway of the lung. Cartilage encircle around 80% of the trachea. The participation of cartilage decreases in lower respiratory system and then no cartilage in bronchioles. In adding up to cartilage the airway epithelium present in spiral bands of smooth muscle, which can dilate or constrict in response to chemicals, irritants or metabolic stimulation.

Kulchitsky cells are neuro endocrine cells which are present in groups throughout trachea bronchial tree .These cells secrete biogenic amines includes dopamine and 5-hydroxy tryptamine (serotonin). These cells are present more in fetus than adults.

BLOOD SUPPLY OF THE

LUNG: PULMONARY

CIRCULATION:

The deoxygenated blood from the right ventricle to the gas exchange which of co2 and oxygenation before blood return to the left atrium for supply to the rest of the body.

BRONCHIAL CIRCULATION:

It starts from the aorta and providing nourishment to the lung parenchyma. The circulation to the lung is unique in its duality and ability to accommodate larger volume of blood at low pressure [(24)].

LUNG DISEASE:

INTERSTITIAL LUNG

DISEASE: INTRODUCTION:

Diffuse interstitial lung disease is consists group of disorders. Different etiologies with common feature of generalized involvement of the lung interstitium. They have heterogenous nature with several common clinical, neurological and histological manifestations.[(2)]

AETIOLOGY AND CLASSIFICATION:

PRIMARY INTERSTITIAL LUNG DISEASE:

It is idiopathic in origin .No secondary cause is identifiable. It is also called cryptogenic fibrosing alveolitis or idiopathic pulmonary fibrosis. This group of idiopathic interstitial pneumonia is classified by clinico- radiological and pathological feature in seven types.

1 .UIP- Usual interstitial pneumonia

2. DIP- Desquamative interstitial pneumonia

3. LIP-Lymphocytic interstitial pneumonia

4. NSIP-Non specific interstitial pneumonia

5. AIP-Acute interstitial pneumonia

6. DAD-Diffuse alveolar disease

7. COP-Cryptogenic organic pneumonia.

SECONDARY INTERSTITIAL LUNG DISEASE:

Secondary ILD have a known etiological cause or an associated with known etiology disease. The secondary ILD commonly present with different connective tissue disorder-progressive systemic sclerosis and Rheumatoid Arthritis. Systemic lupus erythromatous, polymyositis-dermatomyositis syndrome and ankylosing spondylytis are also develop the pulmonary fibrosis.

Occupational exposure to inorganic and hard metals also lead to cause pulmonary fibrosis. silica, asbestos and coal dust will also produce pulmonary fibrosis. sarcoidosis is now commonly present with pulmonary fibrosis.

Several drugs like cytotoxic and non cytotoxic drugs produce ILDs. These drugs are bleomycin, mitomicin, methotrexate, nitrofurantoin, NSAID and opiates. Amiodarone lung toxicity is most commonly produce drug induced ILD.

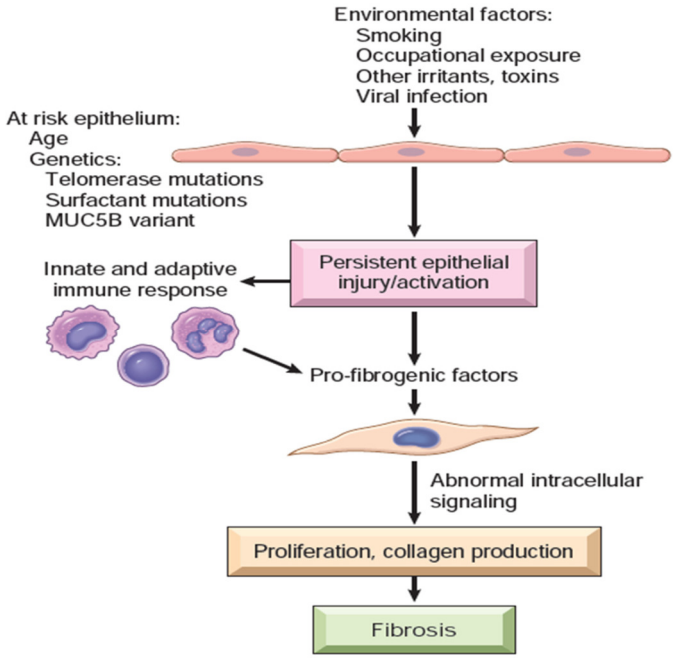
Radiation given for thoracic malignancies that will lead to Iatrogenic ILD. Hypersensitivity pneumonias are acute, subacute or chronic onset which exposure to environmental or occupational antigens like farmer's lung, byssinosis and air conditioners lung.[2]

EPIDEMIOLOGY:

ILDs present about 10% to15% of the patients with respiratory causes in our country. About 50% of the ILD idiopathic in origin. While others are most commonly present with known diseases like connective tissue disease, Usual interstitial pneumonia [2].

PATHOGENESIS:

FIGURE-5



The interstitial lung disease cause is unknown most probably fibrosis arises due to genetic factors are predisposed. Which are prone to damage alveolar epithelial cell injury produced by environmental exposures .

ENVIRONMENTAL FACTORS:

The common factors are smoking which can increase risk of interstitial lung disease is increased due to occupational exposure like farmers, hair dressing and stone-polishing. The exposure to environmental irritants or toxicity will produce rapid alveolar epithelial damage.

GENETIC FACTORS:

One group of genetic lesion occurs in germline loss of function due to mutation in the TERT and TERC genes which encode compounds of telomerase.

Familial IPF is up to 25% present with telomerase gene defects.25% of sporadic telomerase shortening in peripheral pleural lymphadenopathy.

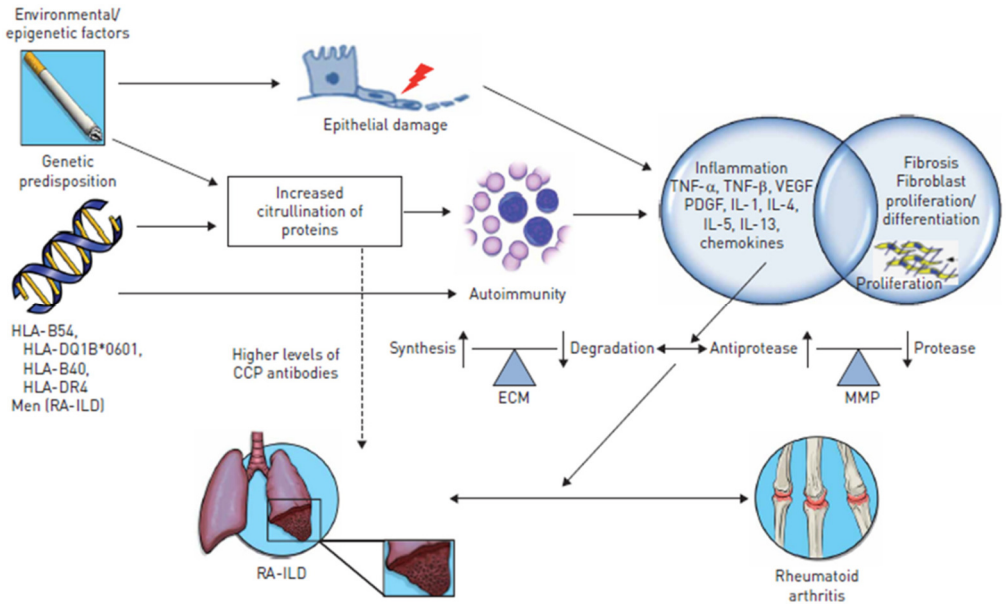
Environmental factors are most commonly produce injuries to alveolar epithelium interact with genetics or aging related factors that will produce persistent epithelial injury.

Factors are severely from injured/activated epithelium. Possibly augmented by factors related from innate and adaptive immune cells responding to "danger" signals produced by damaged epithelium, activate interstitial fibroblasts.

These activated fibroblasts exhibit signaling abnormalities that will lead to increased signaling through the p13k1A1ct pattern. The activated fibroblast synthesis and deposit collagen leading to interstitial fibroblast and eventual respiratory failure.[27]

INTERSTITIAL LUNG DISEASE WITH RHEUMATOID ARTHRITIS:

FIGURE-6



The RA patients have auto antibodies like RF and anticyclic citrullinated peptide(CCP).The auto antibodies present in RA before the clinical disease onset of RA. Both RF and antiCCP antibodies are high titres most commonly will produce ILD.

Anti-ccp antibodies have also develop the airway disease. The form of reactive lymphoid tissue stimulate bronchial alveolar lymphoid tissue (BALT) present in RA patients will produce inflammatory cytokines and antiCCP antibodies. A recent studies shows tissue sample taken from lung and synovial biopsies RA patients discovered identical citrulinated vimentin peptides in both sites.

Smoking play a major role in RA-ILD by promoting citrullination of lung proteins, that will lead to produce anti CCP antibodies. The incidence of RA-ILD is more in persons who have shared epitope HLA-DRB1.[1]

CLINICAL FEATURES:

The prototype idiopathic ILD is mostly present with the older adults of both sexes in the 6th and 7th decade of life .But ILDs secondary to a connective tissue disorders like as RA,PSS or SLE are mostly present with young female patients.

Acute interstitial pneumonia is most commonly produces diffuse alveolar damage causing respiratory distress which is often fatal. The ILDs patients with breathlessness, dry cough associated with malaise, weakness, fever, arthralgia and weight loss are seen commonly with connective tissue diseases. finger clubbing is present with one third of ILD patients. Cyanosis is absent in rest but desaturation periods it will produce severe cyanosis [28].

Physical examination of the chest is present with tachypnoea, reduced chest expansion and intercostals retraction. Breath sounds are vesicular but in late stage of disease bronchial breath sound is heard.

The bi basal dry, end-inspiratory 'velcro' crackles are characteristically heard in patients of Interstitial pulmonary fibrosis. These crackles are produced during snap opening up of collapsed alveoli, which is due to equalization of pressure between alveolar space and proximal bronchiole during inspiration.

CREST syndrome associated with pulmonary hypertension is a primary manifestations, Chronic corpulmonale , chronic congestive failure are complications of ILDs.[28]

INVESTIGATIONS:

ILD is most probably diagnosed by clinical and history examination. Some cardiac disease like cardiac failure and Pulmonary thrombo Embolism (PE) are differential diagnosis. Cardiac diseases are ruled out by electrocardiogram (ECG), chest radiography, Echocardiography, contrast computerized tomography and pulmonary angiography.

CHEST

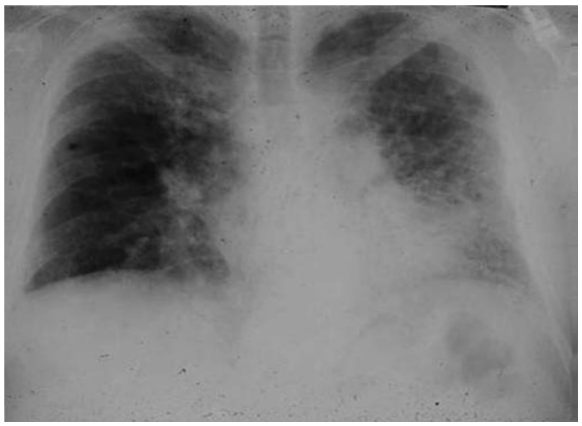
RADIOGRAPHY:

CHEST-X-RAY:

The interstitial infiltrates are present in discrete, linear, nodular or reticulonodular shadows diffusely present in both the lungs. The pulmonary nodule is usually less than 2mm in diameter. In early stages the disease distributed in bibasilar in lungs. Later stages diffuse involvement of whole lungs.

The active stage of diffuse alveolitis is appeard in ground glass appearance. Miliary presentation in whole lung fields are seen in tuberculosis, pneumoconeoses and sarcoidosis. In advanced disease the fibrosis is extensive the lungs get shrunken and reduced in volume. Small uniform sized, quadrangular cysts spaces, patent bronchioles and present like honeycomb lung.[(2)]

FIGURE-7



CHEST –X-RAY SHOWS DIFFUSELY INFILTRATES

HRCT:

HRCT is distinguished the disease pattern and classify the fibrosis. The HRCT picture clearly seen in ILD main features are bibasilar reticular and /or nodular infiltrates , honey combing and absence of lymphadenopathy. HRCT shows subpleural septal thickening, traction bronchiolitis and ground glass appearance are present in Usual interstitial pneumonia.[2]

FIGURE-8

HRCT-INTERSTITIAL LUNG DISEASE

This figure shows high resolution computerized tomography scan reveal non specific interstitial pneumonia with basal ground glass opacity.

PULMONARY FUNCTION TEST:

The ILD most commonly present in restrictive type of on spirometry. The findings are tidal volume small, reduced in vital capacity and total lung capacity. Forced vital capacity (FVC) and Forced expiratory volume (FEV) are reduced in ILD patients. The FEV1/FVC ratio is usually normal or increased [27]. Lung volumes decrease as lung stiffness worsens with disease progression. Reduced diffuse capacity of carbon monoxide (DLCO) and arterial hypoxemia (paO2) are not present in early stage of disease [2].

BRONCHOALVEOLAR LAVAGE (BAL):

To assess the cellular response in BAL . The sarcoidosis and tuberculosis disease are more in lymphocytes.The pulmonary fibrosis is rich in neutrophils The presence of eosinophils due to hypertensive eosinophilia. The BAL contained lymphocytes are potential response to corticosteroids.[2]

HEMATOLOGICAL INVESTIGATIONS:

High ESR in connective tissue diseases, infections, malignancies and systemic vasculitis.

Severe anemia present in alveolar hemorrhage and connective tissue disease.

Mild to moderate leukocytosis is most common in primary and secondary ILD.

Radionucleotide scanning using Gallium67, Positron emission tomography (PET) with glucose FDG isotope to identify the disease process and to estimate response to therapy.[2]

LUNG BIOPSY:

Atypical findings are seen in clinical and radiologically to do for biopsy. The lung biopsy also help to diagnosis and prognosis of the treatment. Transbronchial lung biopsy(TBLB) with the help of Fiber-Optic bronchoscopy(FOB) is usually done in Interstitial pulmonary fibrosis. But the adequate lung tissue taken from through transthoracic or open surgical approach provide better result.[2]

TREATMENT:

Management of primary disease is responsible for a secondary ILD.

OBJECTIVES OF TREATMENT OF ILD:

1. Provide symptom relief
2. Slow down disease progress
3. Prevent complications
4. Improve quality of life

5. Prolong survival

6. Prevent treatment complication

7. End- of-life care- palliative treatment.

TREATMENT OF PRIMARY ILD:

- **ANTI INFLAMMATORY**

  DRUGS: Corticosteroids

  Azathioprine

  Cyclophosphamide

- **ANTI FIBROTIC**

  AGENTS: Colchicines

  Pirtenidone

  Pentoxyphylline

  D-penicillamine TGF-β agonist

  Interferon-γ

- **ANTI OXIDANT AGENTS:**

  N- acetyl cysteine

  Nitric oxide synthase inhibitors

- **SUPPORTIVE AND SYMPTOMATIC TREATMENT:**

  Oxygen

  Pulmonary vasodilatation

  Diuretics

  Antibiotics [2,29].

PULMONARY REHABLITATION:

Interstitial lung disease patients should encourage to participate in Pulmonary Rehabilitation Programme. The recent studies suggest the benefit of tailored exercise programme.

Exercise capacity in the ILD patients correlated with quadriceps strength. The training of the lower extremities increase the exercise capacity .

The ILD patients Quality of life is improved further with specific defects in physical health and perceived social independence. The pulmonary rehabilitation program designed for ILD patients to improve education and psychosocial support elements to get better Quality of life [29]

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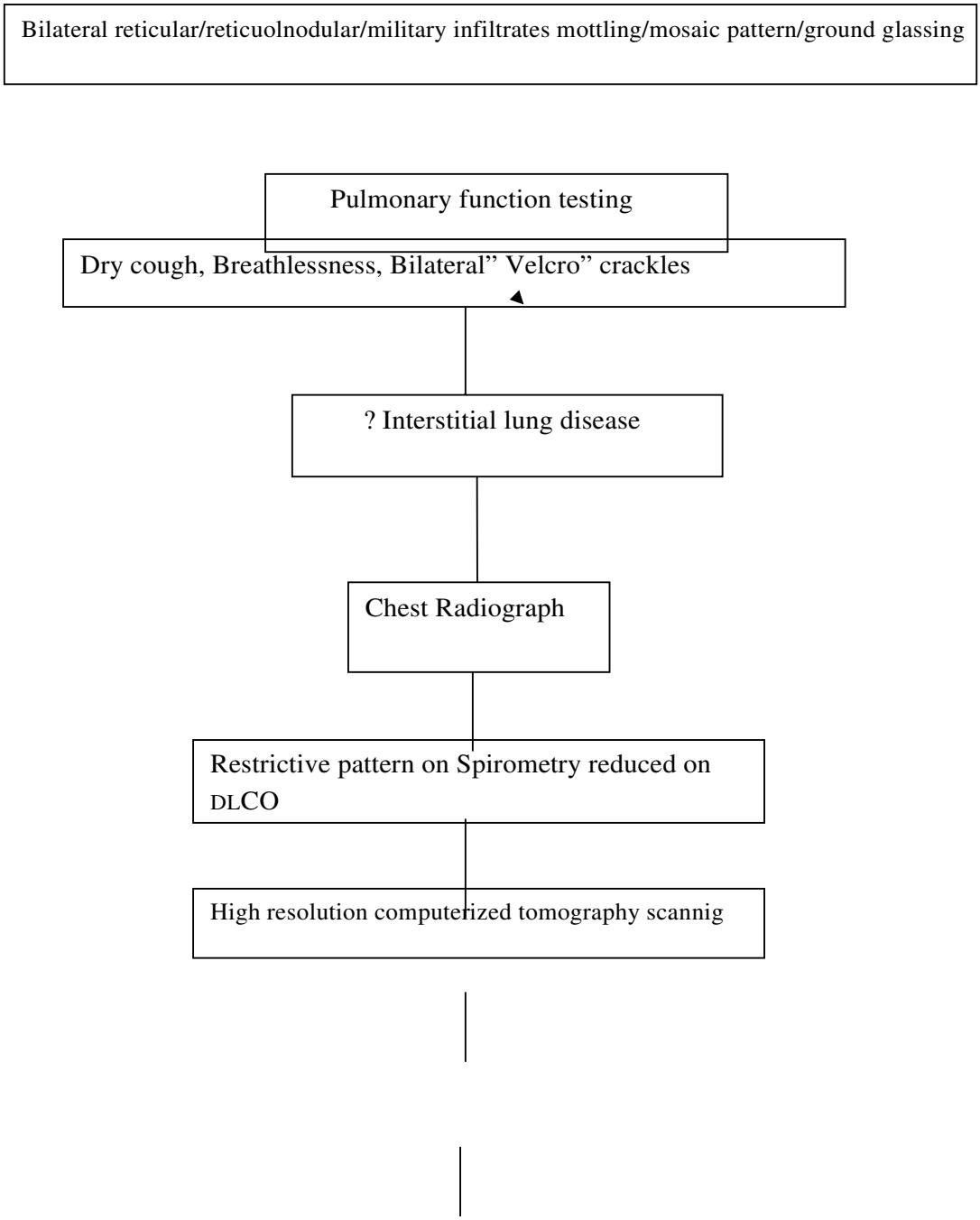
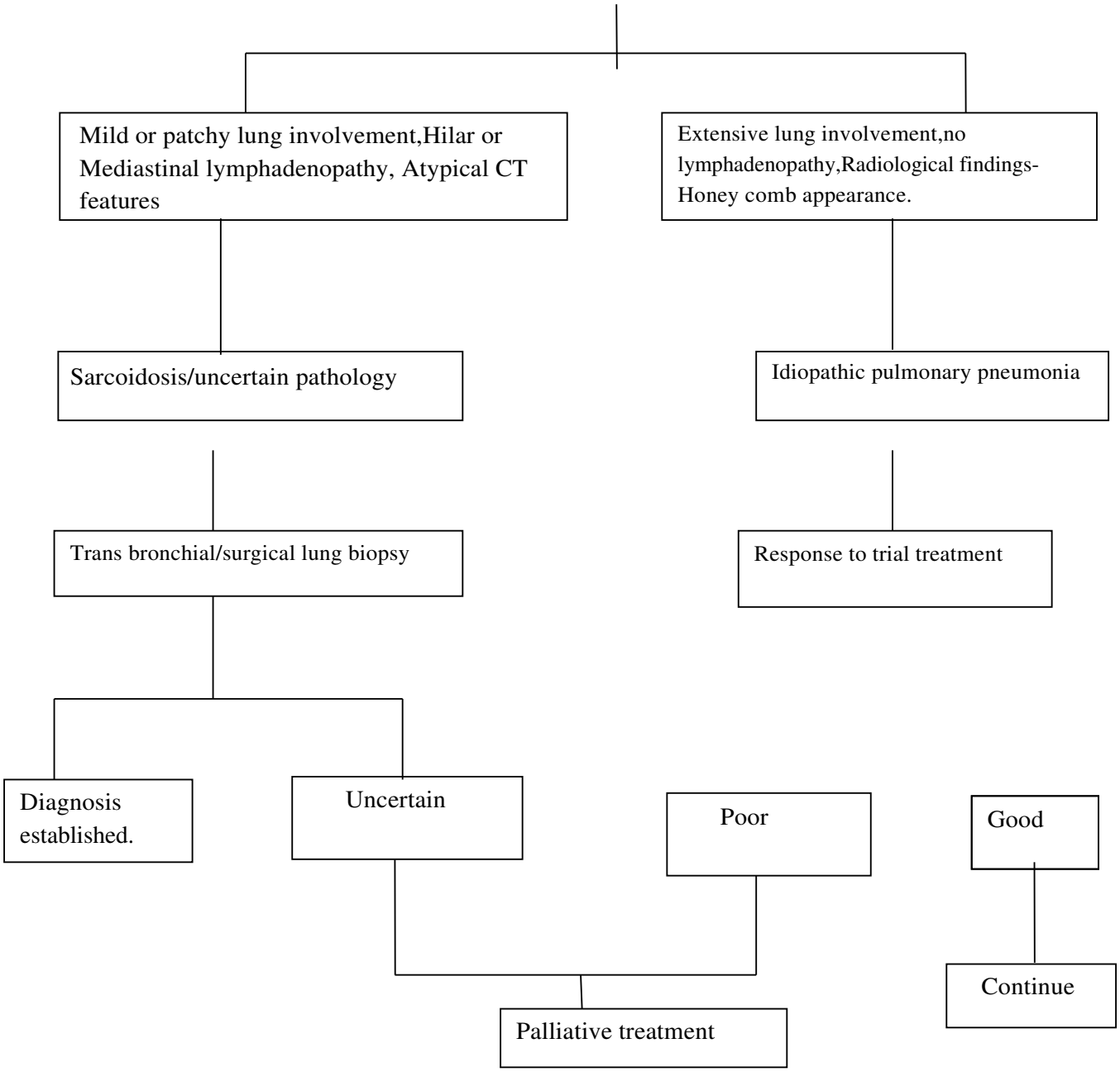

Bilateral reticular/reticuolnodular/military infiltrates mottling/mosaic pattern/ground glassing
Pulmonary function testing
Dry cough, Breathlessness, Bilateral" Velcro" crackles
? Interstitial lung disease
Chest Radiograph
Restrictive pattern on Spirometry reduced on DLCO
High resolution computerized tomography scannig


Mild or patchy lung involvement,Hilar or Mediastinal lymphadenopathy, Atypical CT features
Extensive lung involvement,no lymphadenopathy,Radiological findings- Honey comb appearance.
Sarcoidosis/uncertain pathology
Idiopathic pulmonary pneumonia
Trans bronchial/surgical lung biopsy
Response to trial treatment
Diagnosis established.
Uncertain
Poor
Good
Continue
Palliative treatment

PULMONARY FUNCTION TEST:

Pulmonary function testing commonly includes spirometry, static lung volume measurements and diffusing capacity studies. The measurement of the mechanical properties of the lungs and thorax, airway resistance and compliance [30].

It has been observed that the lung function have mild to moderately reduced before they are appreciated by the patient or clinical signs are observed.

Therefore, the subjective assessment of the severity of the disease is sometimes difficult. It may lead to in adequate treatment interventions and control of the disease.

Measurements of the lung function tests are important in diagnosis and monitoring of treatment of lung disorders [31].

The ability of the gas exchange by lungs depends upon

i. The diaphragm and thoracic muscles which are capable of expanding the thorax and lungs to produce a sub atmospheric pressure.

ii. The airways must be unobstructed so that it allows gas flow into the lungs and reach the alveoli.

iii. The cardiovascular system must circulate blood through the lungs and ventilated alveoli.

Iv .O_2 and CO_2 must be able to diffuse through the alveolar-capillary membrane.[32]

Pulmonary function tests can be divided into categories based on the aspect of lung function they measure

1) Airway function

2) Lung volume and ventilation

3) Diffusion capacity tests

4) Blood gases and gas exchange tests.

5) Cardiopulmonary exercise tests.

6) Metabolic measurements.

Airway function and lung volumes are almost always measured with Spirometry.

SPIROMETRY:

Spirometry is used to measure the rate at which the lung changes volume during forced breathing maneuvers. Spirometry is the most commonly performed pulmonary function test. Spirometry measurement of parameters FVC, SVC&MVV. [30]

In the middle of 18th century, Hutchinson developed a simple water sealed spirometer that allowed measurement of vital capacity. He also observed that VC was related to the standing height of the patient.

In 1679,Borelli first measured the volume of air inhaled by single deep breath. The need for temperature correlation was pointed out by Goodwyn(1788). Thackrah showed the volume of air to be less in women than in men.

Davy (1800) measured by the residual volume by gas dilution method. DuBois and colleagues(1956) developed a method called whole body Plethysmography.

Forced vital capacity is a refinement of the simple VC test. During the1930s ,Barach observed the patients with asthma exhaled more slowly than healthy patients. He noted that airflow out of the lungs was important in detecting obstruction of the airways. He also used kymograph to display VC changes as a spirogram.

In 1950, Gaensler began using a microswitch in conjunction with water sealed spirometer to time FVC. He observed that healthy patients consistently exhaled approximately 80% of their FVC in 1 second and almost all of the FVC in 3 seconds. He used the FEV1 to assess airway obstruction.[33]

In 1955, Leuallen and fowler demonstrated a graphic method to assess airflow. They measured airflow between the 25% and 75% points on a forced expiratory spirogram. This was described as maximal mid expiratory flow rate (MMFR) and now referred to as forced expiratory flow 25%-75%.

In the late 1950s, hyatt and others began using the flow – volume display to assess airway function. The tracing was termed the maximal expiratory flow volume (MEFV)curve. By combining it with an inspiratory maneuver, a closed loop was displayed called the flow-volume loop.

In the 1960s, Wright used the peak flow to monitor asthmatic patients. Peak expiratory flow (PEF) is measured using either a flow – sensing spirometer or a peak flow meter.

Maximal voluntary ventilation (MVV) was described as early as 1941.Cournard and Richards originally called it the maximal breathing

capacity. The MVV gives an estimate of the peak ventilation available to meet physiologic demands

Nowadays, modern computerized pulmonary function systems allow sophisticated data handling band storage, graphic display manueuvers, accurate calculations and enhanced reporting capabilities. They combine physical transducers, analog-to-digital converters, and computer software to process and record physiologic data. Microprocessor-based spirometers are now small enough to be handheld and portable [33].

TYPES OF SPIROMETERS:

Broadly there are two types of spirometers:

I. VOLUME DISPLACEMENT SPIROMETER:

These records the amount of air exhaled or inhaled within a certain time. These widely used types of volume spirometer are

1) Water seal spirometer

2) Dry rolling seal spirometer

3) Bellows spirometer.

II. **FLOW SENSING SPIROMETER OR PNEUMOTACHOMETER**:

These measures how fast the air flows in or out as the volume of air inhaled or exhaled increases.

The most common types of flow spirometers are

1) Rotating vanes (turbines)

2) Pressure differential flow sensing spirometers

3) Hot wire anemometers

4) Pilot tube flow sensing spirometers.[31]

Spirometry can be performed in either the sitting or standing position for adults and children. The use of nose clips is recommended for spirometric measurements that require re breathing, even if just for few breaths.[31]

INDICATIONS:

1. Detect abnormalities in the lung function .

2. Quantify the severity or stage of known lung disease.

3. To monitor the prognosis of disease and treatment response.

4. Assess the risk for peri operative pulmonary complications.

5. Monitor the effects of exposure to drugs or toxins affecting the lungs.[30]

CONTRAINDICATIONS:

1.Cardiovascular disease-

MI 2, Hemoptysis

3. Pneumothorax.

4. Nausea

5. Vomiting. [30]

SPIROMETRY QUALITY ASSURANCE:

- Equipment calibration
- Technique validation

EQUIPMENT CALIBRATION:

The American thoracic society(ATS)guidelines specify that spirometers should be capable of measuring volumes of 8 L or more and capturing exhalation maneuvers for at least 15 seconds.

Volume accuracy should be at least ±3.5% or ±0.065% L, with the measured flow range between 0 and 14L/second.

Flow measurements should be accurate within ±5% of the true value over a range of -14 to +14 L/second with a sensitivity of 0.025L/second. [30]

TABLE-5

CALIBRATION TESTS FOR SPIROMETRY EQUIPMENT:

TEST	MINIMUM INTERVAL	ACTION
volume	daily	Calibration with a calibrated 3-L syringe
Volume linearity	quarterly	1-L increment with a calibrated syringe over entire volume range.
Flow linearity	weekly	Test at least three different flow ranges.
software	New versions	Log installation date and perform test using biologic controls and known subject.

TECHNIQUE VALIDATION:

The goal is to obtain at least three acceptable error free maneuvers that are repeatable.

An acceptable maneuver must be free from artifacts, exhibit a good and forceful start and achieve complete exhalation.

ACCEPTABILITY AND REPEATABLITY CRITERIA:

The spirogram acceptable :

- Free from artefacts;-coughing/breathing during the maneuver.

  -early termination or cut-off

  -submaximal effort.

- Exhibits a rapid, forceful start:

  -time to peak flow<120msec.

  -back extrapolated volume <55 of FVC or 150ml.whichever is greater.

- Achieve complete exhalation:

  -duration of at least 6 sec(COPD patients may need >10 second),or

  -attainment of a plateau (<25mL change in volume for >1second.

➢ Results are repeatable if after three acceptable spirograms have been obtained:

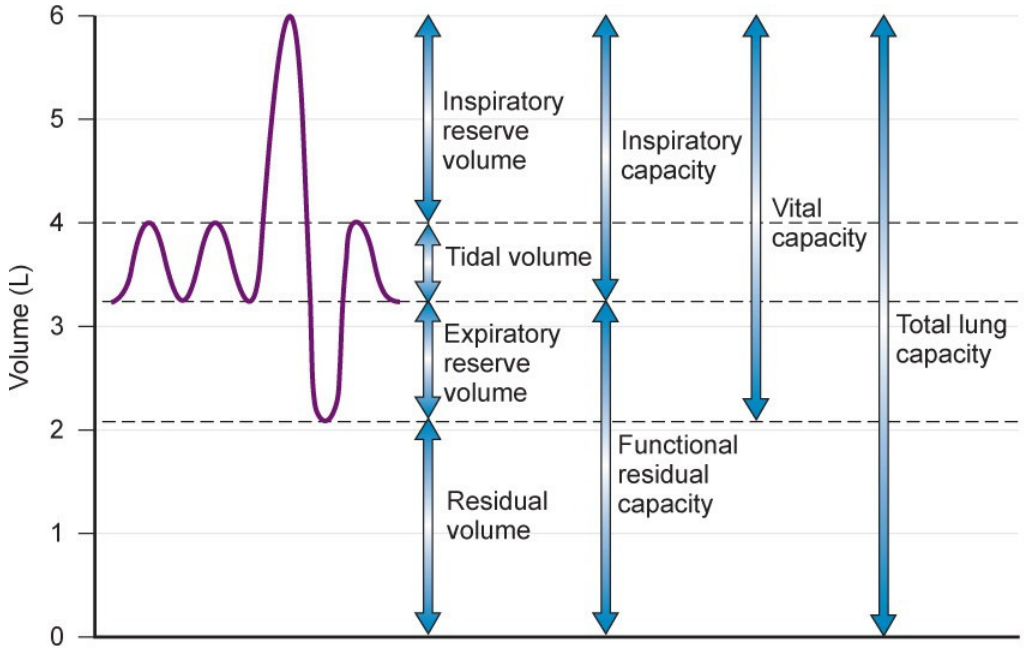
- The two largest values of FVC must be with in 0.150 L of each other.
- The two largest values of FEV_1 must be with in 0.150 L of each other.

(30)

LUNG VOLUMES AND CAPACITIES:

Lung volume determination usually includes the VC and its subdivisions, along with functional residual capacity. From these two basic measurements, the remaining lung volumes and capacities can be calculated. The most common reason for measuring lung volumes is to identify restrictive lung disease. Lung volumes are almost airways measures in conjunction with spirometry.

FIGURE-9



The lung volumes are

1. Tidal volume is the volume of air inspired or expired during quiet breathing and is about 500ml.

2. The amount of air inspired with maximum inspiratory effort above the normal tidal volume is called inspiratory reserve volume; it is about 3000ml.

3. The expiratory reserve volume is the volume of air expired with maximum expiratory effort after the end of a normal tidal expiration; this normally amounts to about 1100ml.

4. The volume of air remaining in the lungs after the forceful expiration is known as residual volume; it is normally about 1200ml.

The pulmonary capacities are

1. The maximum amount of air inspired after completing the tidal expiration is defined as inspiratory capacity and is about 3500ml.

2. The functional residual capacity is the amount of air remaining in the lung at the end of normal expiration and is about 2300ml.

3. The vital capacity is the maximum amount of air expired forcefully after a maximum inspiratory effort and is about m4600ml.

4. The total lung capacity is the volume of air present in the lung after a maximum inspiration and is about 6 litres [34].

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FORCED VITAL CAPACITY:

The most common spirometry test is the FVC. Forced expiratory volume in 1,3&6 seconds(FEV $_1$, FEV$_2$&FEV6)are all volumes measured at specific times during the forced exhalation.

A normal individuals is able to exhale at least 75% of FVC in 1 second and generally 95% or more in 3 seconds [30].

FLOW-VOLUME LOOPS:

Most electronic spirometers also can display and record the FVC maneuver as a plot of flow versus volume, typically referred to as a flow-volume loop.

To produce a complete flow volume loop, the patient must be instructed to take a full forced inspiration to TLC and after the forced exhalation maneuver.

The spirometer then records both the inspiratory and expiratory efforts.

The expiratory component is called the maximal expiratory flow-volume curve(MEFV) is plotted above the horizontal zero flow line.

The inspiratory component is maximal inspiratory flow-volume curve (MIFV) is recorded below the zero flow line.

Spirometers record the FEF at 25%, 50% and &75% of the FVC [30].

MAXIMAL VOLUNTARY VENTILATION:

The MVV is the maximal volume of air a subject can breathe over a specified period of time, usually 12 seconds.

The 12-second volume then is multiplied by 5 to extrapolate wha could be achieved in 1minute.the value expressed in litres per minute.

The MVV is affected by the strength of the respiratory muscles, compliance of the lungs and thorax, inspiratory and expiratory airway resistance and patient motivation &effort.

To estimate a patient's MVV, multiply the measured FEV_1 by 40 [30].

FIGURE-10

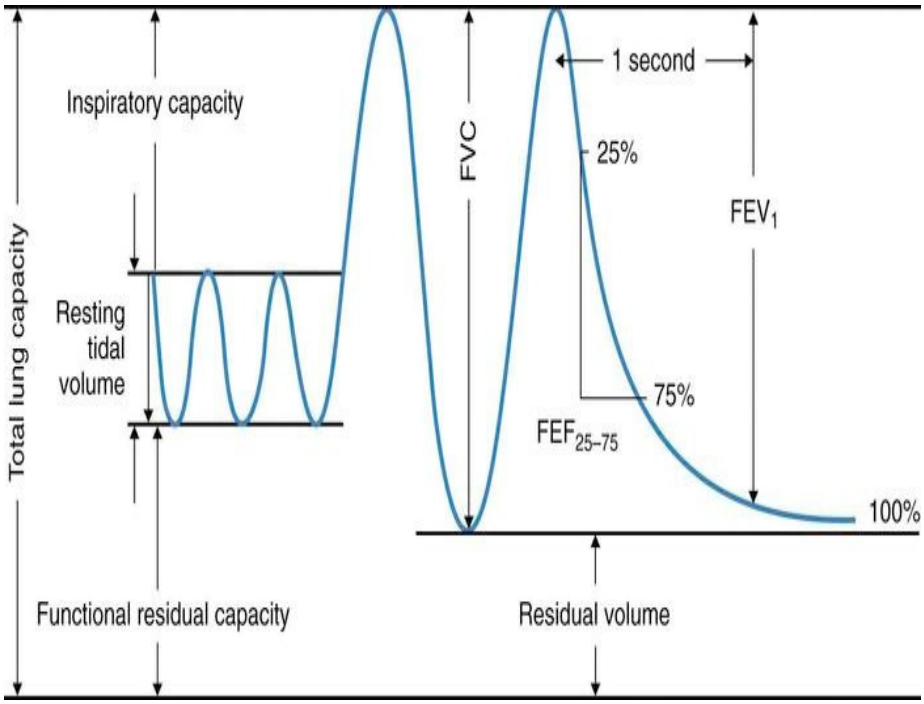


TABLE-6

PARAMETERS TYPICALLY MEASURED DURING SPIROMETRY:

PARAMETER	ABBREVIATION	DEFNITION
Forced vital capacity	FVC	Total volume of air that can be exhaled during maximal forced expiration effort.

Forced expiratory volume in 1 second	FEV_1	Volume of air exhaled in the first second after a maximal forced inhalation.
Ratio of FEV_1 TO FVC	FEV_1/FVC	Proportion or percentage of the FVC expired during the first second of the maneuver.
Forced expiratory volume in 3 seconds	FEV3	Volume of air exhaled in 3 seconds after a forced maximal inhalation
Forced expiratory volume in 6 seconds	FEV6	Volume of air exhaled in 6 seconds after a forced maximal inhalation
Peak expiratory flow	PEF	Maximal expiratory flow, typically achieved within 120 mseconds of the start of the forced exhalation.
Maximal mid expiratory flow	FEF 25-75%	Average flow occurring between 25% and 75% of the FVC.

TABLE-7

TYPICAL PATTERN OF LUNG IMPAIRMENT: [35]

MEASUREMENT	OBSTRUCTIVE	RESTRICTIVE
FVC(L)	N to ↓	↓
FEV1(L)	↓	↓
FEV1/FVC (%)	N to ↓	N to ↑
FEF 25-75(L/s)	↓	N to ↓
PEF (L/s)	↓	N to ↓
FEF 50(L/s)	↓	N to ↓
Slope of FV CURVE	↓	↓
MVV (L/s)	↓	N to ↓

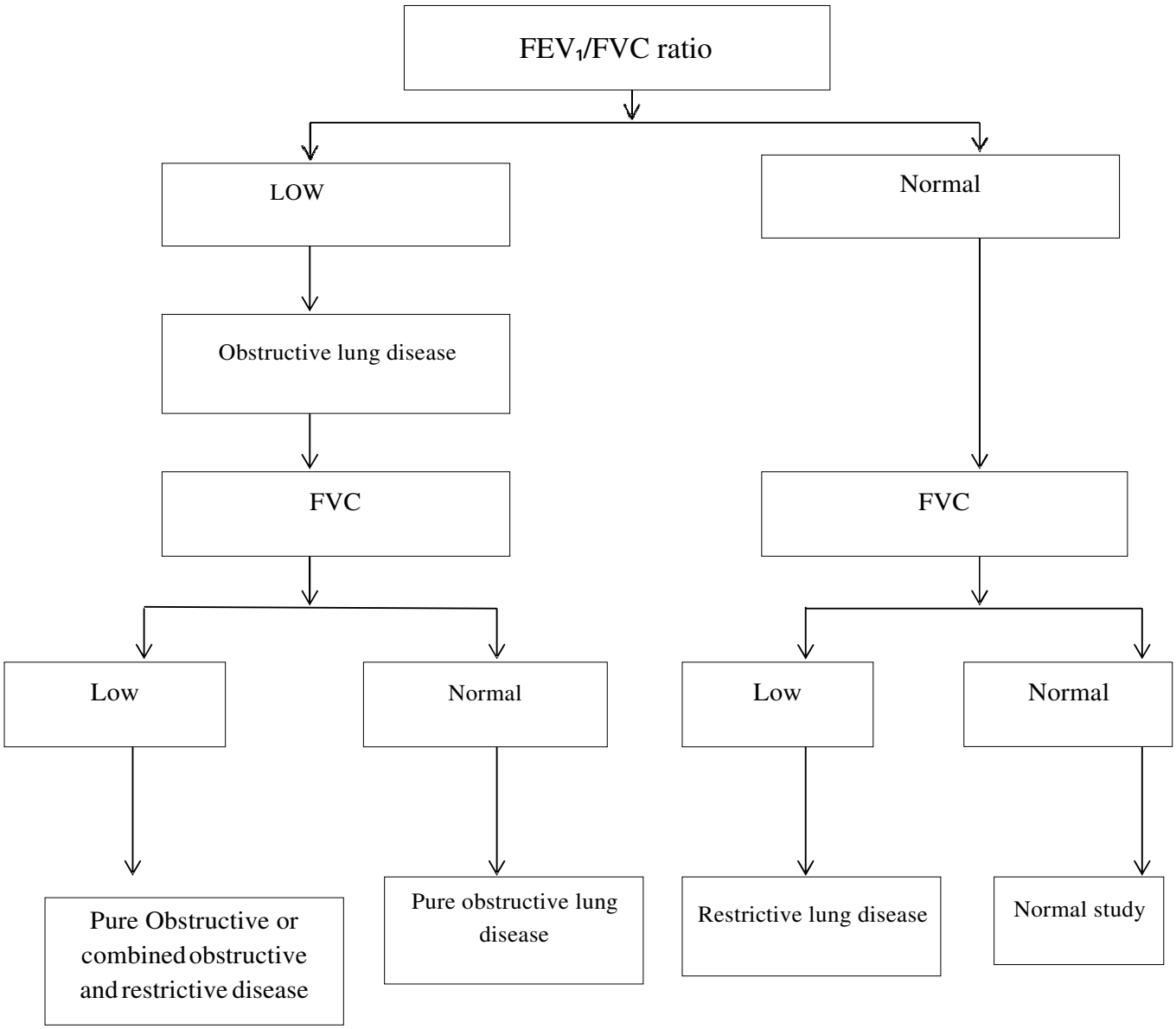
TABLE- 8

METHODS OF GRADING THE SEVERITY OF OBSTRUCTIVE AND RESTRICTIVE DISORDERS: [35]

Grading of severity of any spirometric abnormality based on FEV_1	
After determining the pattern to be obstructive ,restrictive or mixed , FEV_1 is used to be grade severity:	
MILD	FEV_1 >70%
MODERATE	60-69%
MODERATELY SEVERE	50-59%
SEVERE	35-49%
VERY SEVERE	<35%

Traditional method of grading the severity of obstructive and restrictive disorders	
Obstructive disorder (based on FEV_1) – ratio >0.7	
May be physiologic variant	$FEV_1 \geq 100$ (%PREDICTED)
MILD	70-100%
MODERATE	60-69%
MODERATELY SEVERE	50-59%
SEVERE	35-49%
VERY SEVERE	<35%
Restrictive disorder(based on TLC)	
MILD	TLC >70 (%PRED)
MODERATE	60-69%
SEVERE	<60%
Restrictive disorder (based on FVC)	
MILD	FVC > 70 (%PRED)
MODERATE	60-69%
MODERATELY SEVERE	50-59%
SEVERE	35-49
VERY SEVERE	<35

INTERPRETATION OF SPIROMETRY RESULTS [31]



METHODS AND MATERIALS

40 healthy volunteers were randomly recruited from the general population residing at Thanjavur.40 Rheumatoid arthritis patients were selected from the rheumatology outpatient department of age group 25-55 years with duration of Rheumatoid arthritis less than 5 years. This was a case- control type of study done during the period of June 2016-2017.

For this study, 40 healthy controls and 40 Rheumatoid arthritis patients were selected.

An informed written consent was obtained from all the participants prior to their participation in the study. The study protocol was approved by the institutional ethical committee of Thanjavur Medical College.

Anthropometric measurements like Height, Weight and BMI were calculated. Rheumatoid factor for the participants was measured by Turbidometry method and C-reactive protein by Turbidometric Immunoassay method.

Detailed history and thorough clinical examination was carried out.

INCLUSION CRITERIA:

Rheumatoid Arthritis patients on anti-Rheumatoid drugs and having RA for less than 5 years duration of age group 25-55 years . Thorough clinical examination and history were obtained from the subjects in order to determine the health status of the individual.

EXCLUSION CRITERIA:

Diabetes Mellitus,

Alcoholism with Other connective tissue

disorders , Metabolic disorders ,

Neuropathies,

Pulmonary

Tuberculosis,

Carcinoma Lung.

Pulmonary function tests were done using computerized spirometer which was standardized according to American Thoracic Society Performance criteria [Spiro Excel –Digital Spirometer - medicaid systems].

The pulmonary function parameters like Forced vital capacity [FVC], FEV 1, FEV_1 / FVC %, Slow vital capacity [SVC] and Maximum voluntary ventilation [MVV] are recorded. The pulmonary function test was performed 3 times on the same day in sitting posture with two minutes interval and the best of the three was taken.

Blood samples were drawn for estimating the Rheumatoid factor, C-reactive protein. The pulmonary function data were represented in three columns. These columns show the predicted values obtained during testing and the percent of predicted values for each test. A common method of comparison is to compute a percentage of the predicted value.

PRECAUTIONS:

i. The subject must be comfortable and relaxed.

ii. The apparatus should be sterilized and cleaned properly.

iii. The subject should sit with his spine erect and nostril closed.

iv. The mouth piece is placed in the subject's mouth in such a way that the mouth piece remains fitted between the teeth and lips.

v. The subject should be demonstrated and trained about the different maneuver.

vii. Minimum three recordings should be taken for each maneuver at a gap of two minutes each and the best of the three should be taken.

PROCEDURE:

FORCED VITAL CAPACITY:

Forced vital capacity(FVC) is the maximum volume of air expired when the subject exhales forcefully and rapidly as possible after maximal inspiration.FVC is followed by Forced inspiratory vital capacity (begins with maximal expiration and ends with maximal inspiration)and form a flow volume loop.[33]

CRITERIA FOR ACCEPTABILITY:

1. Maximal effort; no cough or glottis closure during the first second; noleaks or obstruction of mouth piece.`
2. Good start- of-test; extrapolated volume < 5% of FVC or 150ml.
3. Duration- 6 seconds of exhalation.
4. Three acceptable spirograms are obtained; two largest FVC values within 200ml and two largest FVC values within 200ml and two largest FEV_1 values within 200ml are taken.

SLOW VITAL CAPACITY:

The subject is instructed to inhale and exhale normally to record the tidal volume. Then the subject is asked to breathe in as much as possible after the normal expiration and exhale maximally to record inspiratory and expiratory volume.

Criteria for acceptability:

1. Two acceptable VC maneuvers should be obtained and volumes within 200ml.
2. VC should be within 200ml of FVC value.[33]

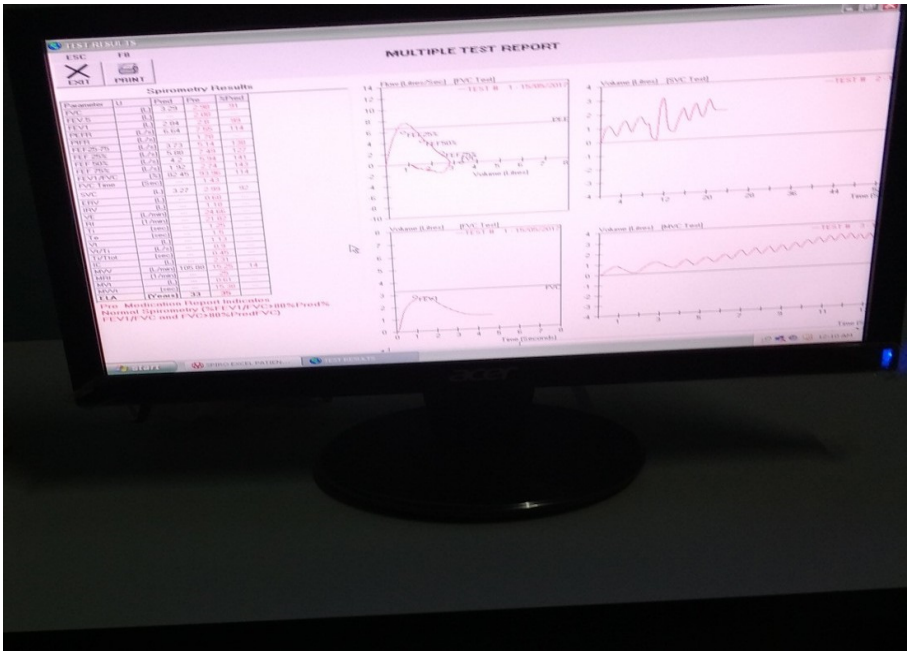
MAXIMUM VOLUNTARY VENTILATION:

The subject is asked to breathe as deeply and as rapidly as he can for 15 seconds.

Criteria for acceptability:

1. Volume – time tracing shows continuous, rhythmic effort for at least 12seconds.
2. End- expiratory lung volume is relatively constant.
3. Two acceptable maneuvers are obtained; MVV values are within 10%
4. MVV is approximately equal to 35×FEV_1. [33]

FIGURE-11

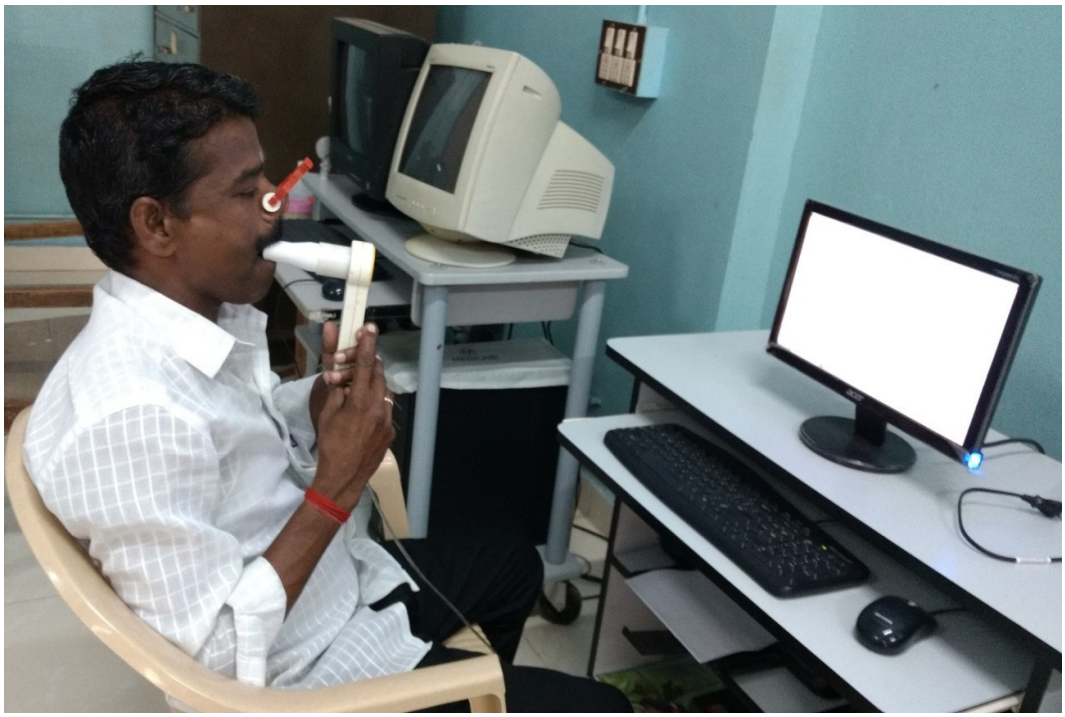


COMPUTERIZED DIGITAL SPIROMETRY-SPIRO EXCEL

FIGURE-12

SEMI AUTOANALYZER

FIGURE-13



RESULTS

In this case-control study which was conducted in Thanjavur Medical College, totally 80 subjects were participated .Out of 80 participants 40 were Rheumatoid arthritis patients (less than 5 years) forming the study group and the remaining 40 were normal subjects forming the control group.

The participant's anthropometric, biochemical and the lung function parameters were analyzed by arithmetic mean and standard deviation. The mean values of pulmonary function parameters of the RA patients were compared with healthy controls using Independent student # t# test.

Statistical analysis was done by using the Statistical Package for Social Sciences (SPSS) X version. The results were analyzed by using Independent student # t# test.

$P < 0.05$ was considered as statistically significant.

Descriptive analysis was done for all the parameters and are tabulated in Table-1.

TABLE - 1

DESCRIPTIVE STATISTICS

	CONTROL &STUDY (n=80)			
	Minimum	**Maximum**	**mean**	**S.D**
Age (years)	30	52	40.24	6.070
Height(cm)	145.00	172.00	158.33	6.344
Weight(kg)	45.00	76.00	59.48	6.465
BMI(kg/m²)	16.50	27.30	23.63	1.810
RAfactor (IU/ml)	1.80	302.20	48.72	73.46
CRP(mg/dl)	0.10	1.40	0.508	0.30
FEV1 (L)	65	115	77.80	8.09
FVC (L)	61	124	80.02	12.40
FEV1/FVC (%)	57	148	98.80	15.49
FEF25-75% (L/s)	69	124	97.69	7.73
PEFR (L/s)	63	115	87.49	9.75
MVV(L/min)	52	140	80.17	14.71

The baseline characteristics of the control and study group are shown in the table.

TABLE -2

ANTHROPOMETRIC AND CLINICAL PARAMETERS OF CONTROL AND STUDY GROUPS

	CONTROL (n=40)				STUDY (n=40)			
	Min	**Max.**	**Mean**	**S.D**	**Min**	**Max.**	**Mean**	**S.D**
Age (yrs)	30	52	40.73	5.901	30	52	39.75	6.271
Height (cm)	145.00	172.00	160.275	6.352	145.00	165.00	156.400	5.786
Weight (kg)	48.00	76.00	61.625	6.511	45.00	70.00	57.350	5.736
BMI (Kg/m^2)	20.20	27.20	23.852	1.754	16.50	27.30	23.417	1.861
RA factor IU/ml	1.80	13.10	7.742	2.940	12.40	302.20	89.700	86.477
CRP mg/dl	0.20	1.10	0.507	0.249	0.10	1.40	0.510	0.347

The mean (±SD) of Rheumatoid Factor of control group is 7.742±2.940 and for the study group is 89.700±86.477.This table shows study group having high titre of RA factor.

TABLE -3

PULMONARY FUNCTION PARAMETERS OF CONTROL AND RA PATIENTS:

	control (n=40)				Study (n=40)			
	Min	**Max.**	**Mean**	**S.D**	**Min**	**Max.**	**Mean**	**S.D**
FEV1(L)	68	115	79.72	9.109	65	94	75.88	6.485
FVC(L)	68	124	83.18	13.838	61	98	76.87	9.985
FEV1/FVC(%)	57	148	97.90	16.531	73	136	99.70	14.532
FEF25-75(L/s)	69	124	99.85	8.220	85	113	95.53	6.645
PEFR(L/s)	63	115	89.90	10.536	65	98	85.08	8.365
MVV(L/min)	52	140	83.93	15.641	56	99	76.42	12.848

The mean (±SD) of the pulmonary function parameters of both study group and control group are shown in the table - 3.

Table – 4 and Figures 14 – 17 show anthropometric and clinical parameters of controls and RA patients.

TABLE-4

ANTHROPOMETRIC AND CLINICAL PARAMETERS OF CONTROLS AND RA PATIENTS:

	CONTROL(N=40)	STUDY(N=40)	P VALUE
	MEAN ± SD	MEAN±SD	
AGE(yrs)	40.73 ±5.901	39.75±6.271	0.476
HEIGHT(cm)	160.275±6.352	156.40±5.785	0.006*
WEIGHT(kg)	61.625±6.511	57.35±5.735	0.003*
BMI(Kg/m^2)	23.85±1.754	23.41±1.861	0.285
RA factor IU/ml	7.74±2.940	89.70±86.477	0.0001*
CRP mg/dl	0.507±0.249	0.510±0.347	0.971

(*P value less than 0.05 was considered to be statistically significant)

The mean (±SD) of C-Reactive protein of control group is 0.507±0.249 and the study group is 0.510±0.347,there is no significant change in CRP level between the control and study group .

FIGURE-14

COMPARISON BETWEEN THE CONTROLS AND RA GROUP – WITH PARAMETERS OF AGE AND BMI

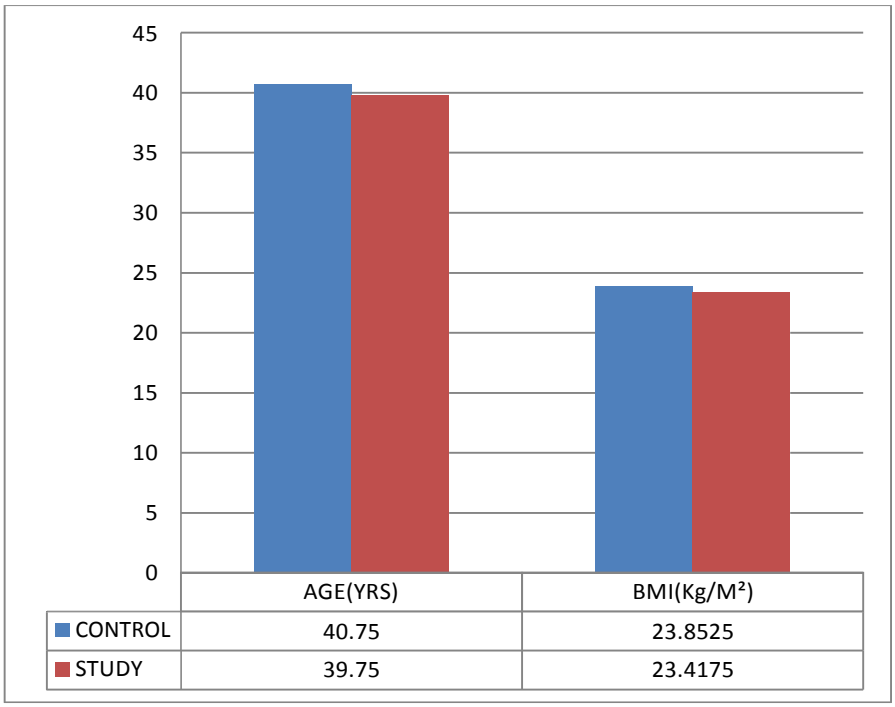


FIGURE-15

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS – WITH PARAMETERS OF HEIGHT AND WEIGHT

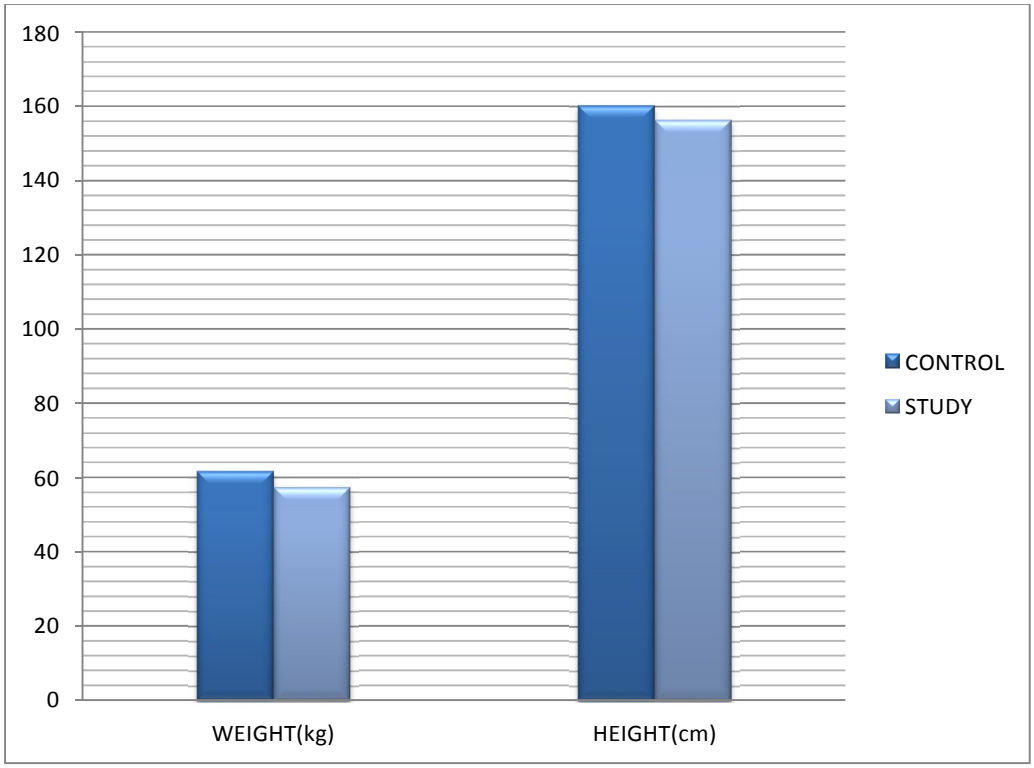


FIGURE -16

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETER OF C-REACTIVE PROTEIN

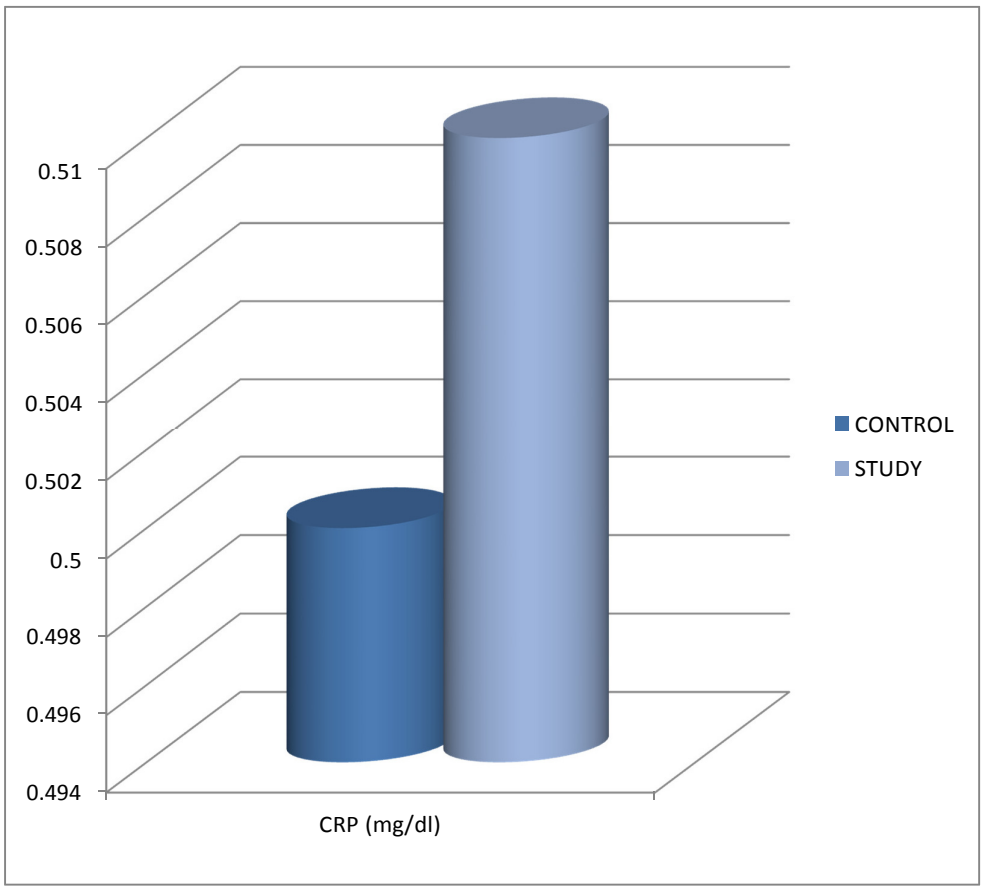


FIGURE-17

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETER OF RA FACTOR (IU/dl)

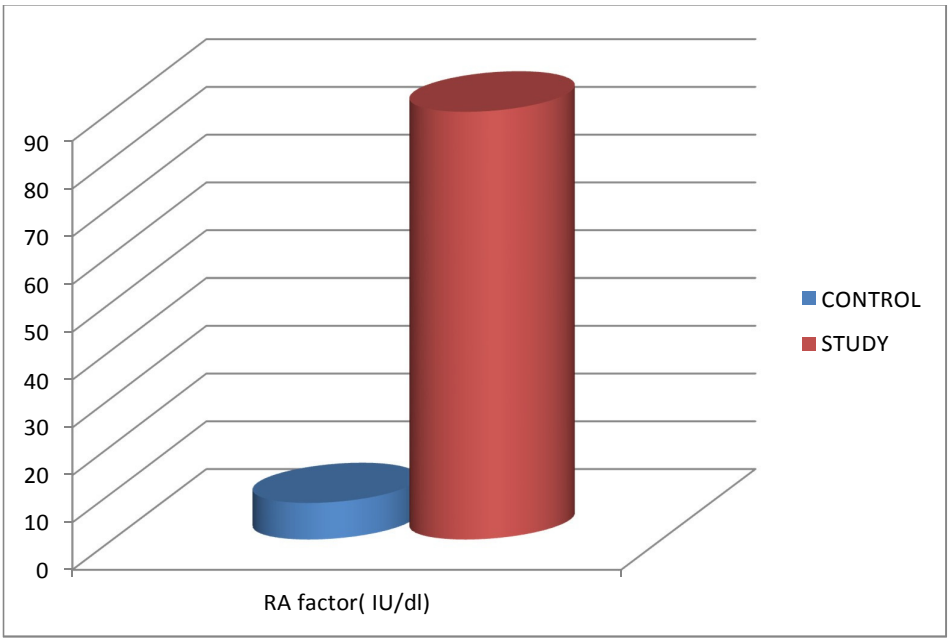


Table – 5 and Figures 18 – 25 shows the comparison of pulmonary function test parameters between the controls and study groups.

TABLE – 5

COMPARISON OF PULMONARY FUNCTION TEST PARAMETERS BETWEEN THE CONTROLS AND RA PATIENTS:

	CONTROL(n=40)	STUDY(n=40)	P value
	MEAN ± SD	MEAN ± SD	
FEV_1(L)	79.72±9.109	75.88±6.485	0.032*
FVC(L)	83.18±13.83	76.87±9.985	0.022*
FEV_1/FVC(%)	97.90±16.53	99.70±14.532	0.606
FEF25-75(L/s)	99.85±8.22	95.53±6.645	0.012*
PEFR(L/s)	89.90±10.53	85.08±8.365	0.026*
MVV(L/min)	83.93±15.64	76.42±12.848	0.022*

(*P value less than 0.05 was considered to be statistically significant)

The mean (±SD) of FEV_1 for the control group are 79.72±9.109 and for RA group are 75.88±6.485.It was found to be significantly reduced (P=0.032).

The mean (±SD) of FVC for the control group is 83.18±13.83 and for RA patients group is76.87±9.985 .The mean FEF 25-75% for the control group is 99.85±8.22 and for study group 95.53±6.645 .The mean values of FEV_1 and FEF 25-75% are found to be reduced in RA group when compared to controls are statistically significant.

The mean (±SD) of FEV1/FVC (%) for the control group is 97.90±16.53 and for RA patients group 99.70±14.53. The mean values of FEV1/FVC (%) are found to be mild increased but not statistically significant.

The mean (±SD) of PEFR for control group 89.90±10.53 and for the study group 85.08±8.365.The mean (±SD) of MVV for control group 83.93±15.64 and for RA group 76.42±12.848.The mean values of PEFR and MVV are reduced in RA patients when compared with controls are statistically significant.

FIGURE-18

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETER OF FORCED VITAL CAPACITY (FVC)

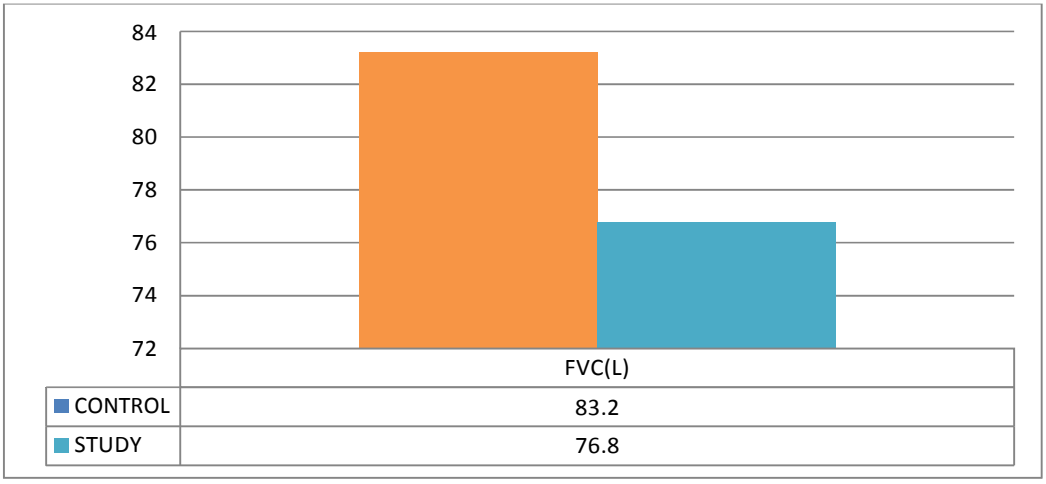


FIGURE-19

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETER OF FORCED EXPIRATORY VOLUME 1 SECOND

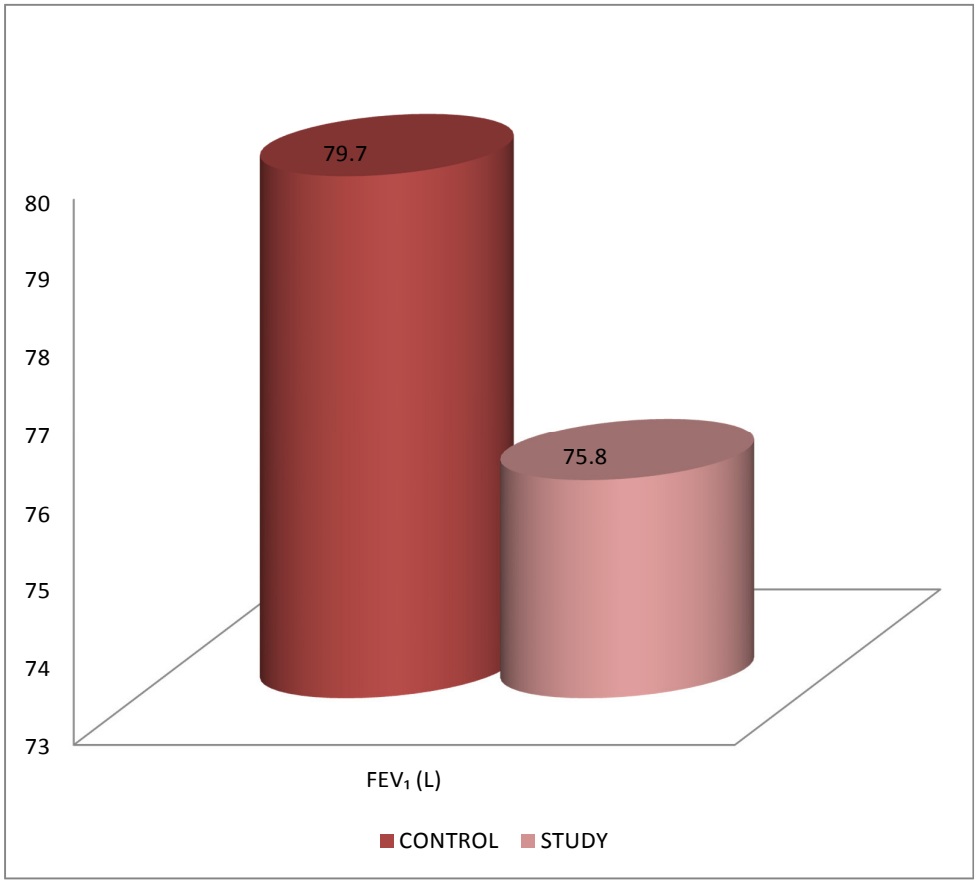


FIGURE-20

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETER OF FEV_1/FVC (%)

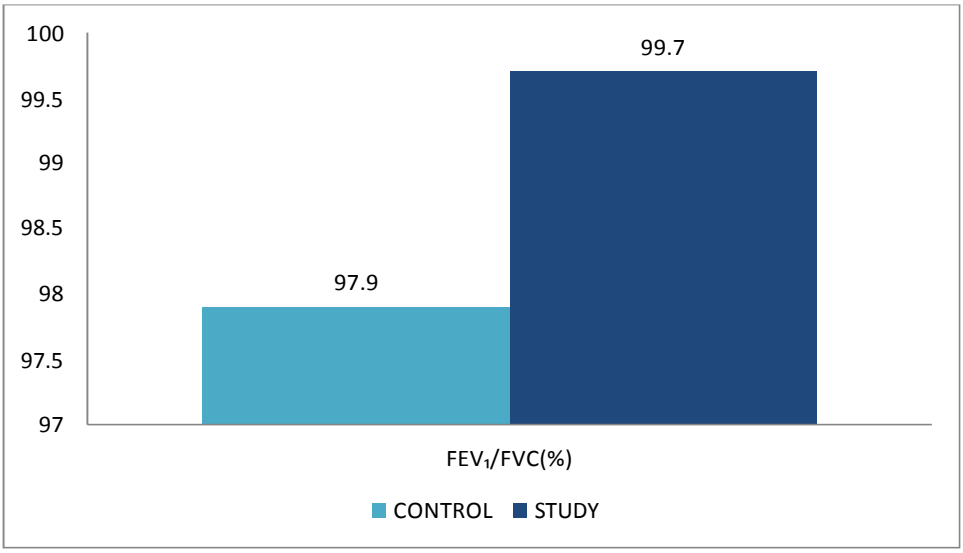


FIGURE-21

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETER OF FEF 25-75%

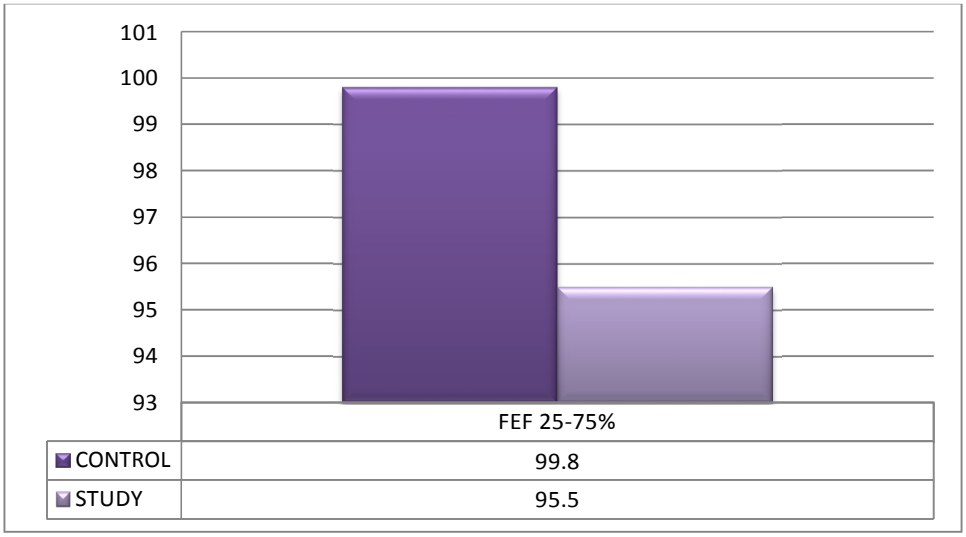


FIGURE-22

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETER OF PEFR(L)

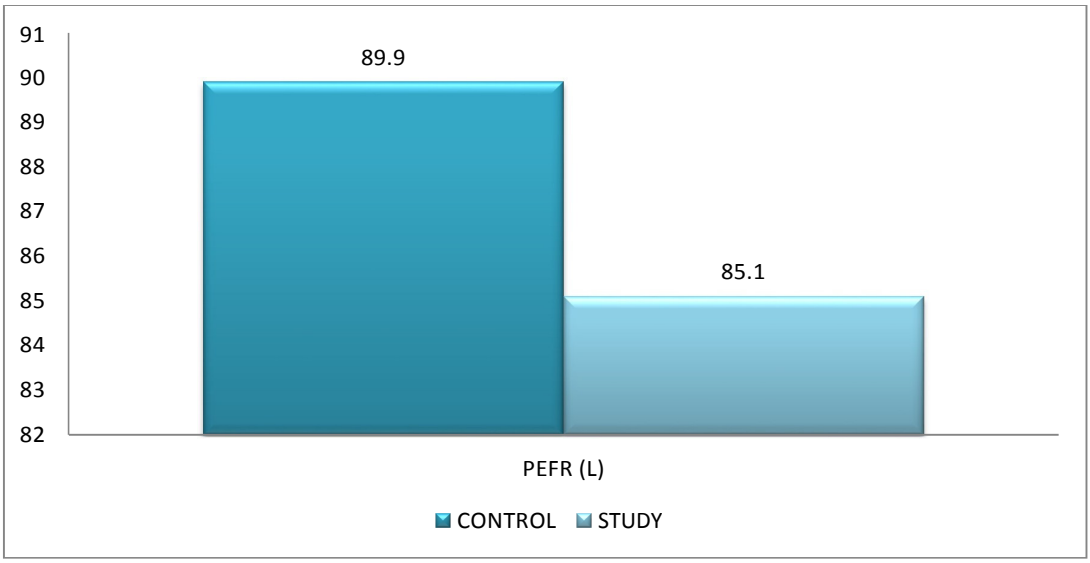


FIGURE-23

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETER OF MVV

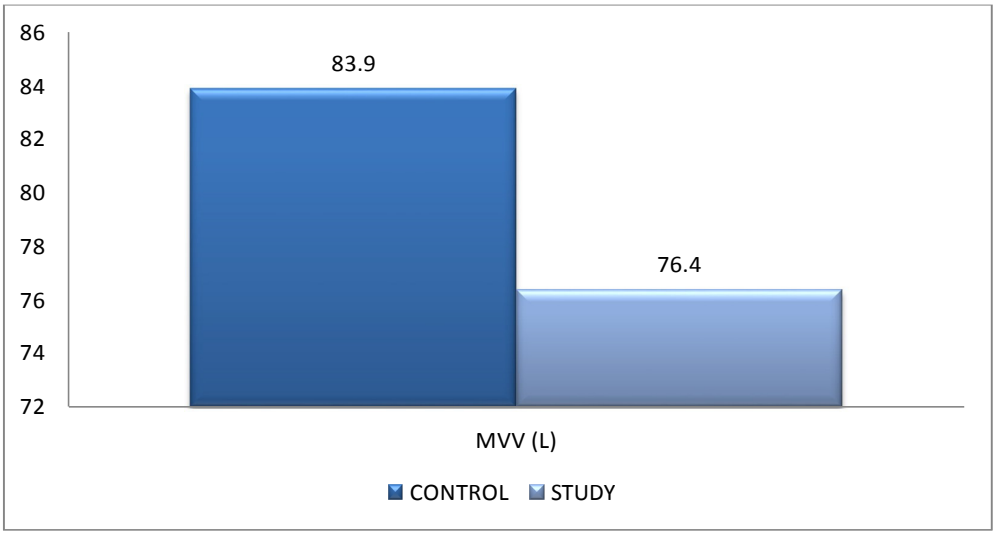


FIGURE-24

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS – WITH PARAMETERS OF PULMONARY FUNCTION TESTS

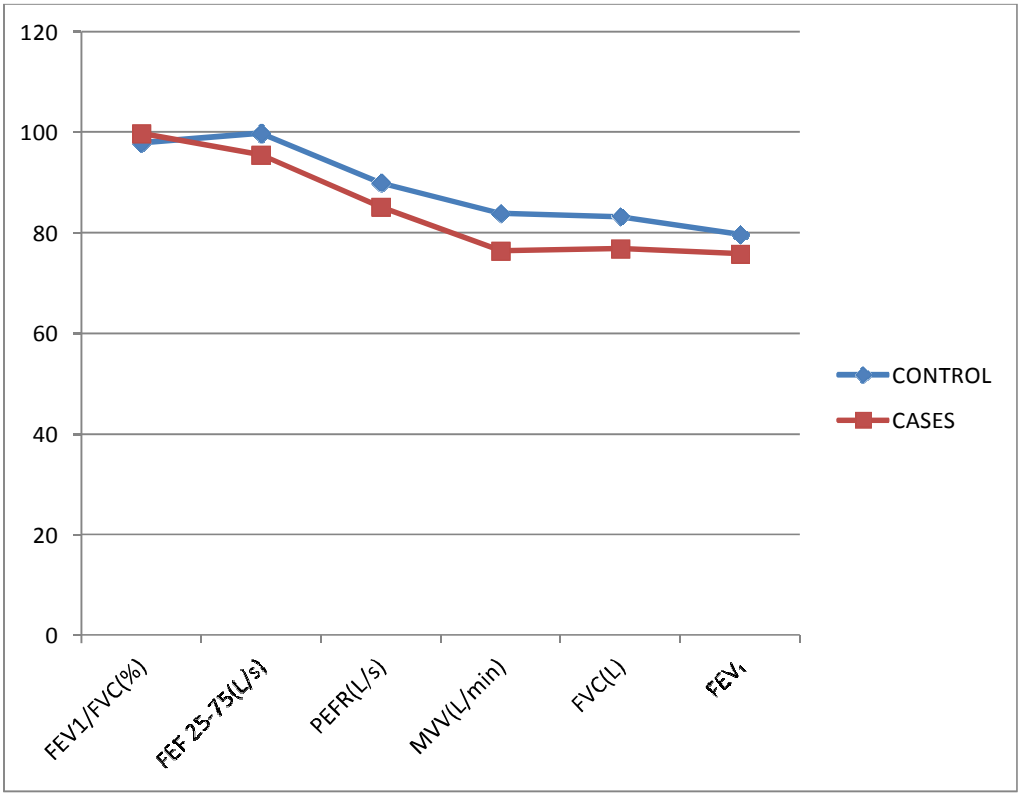
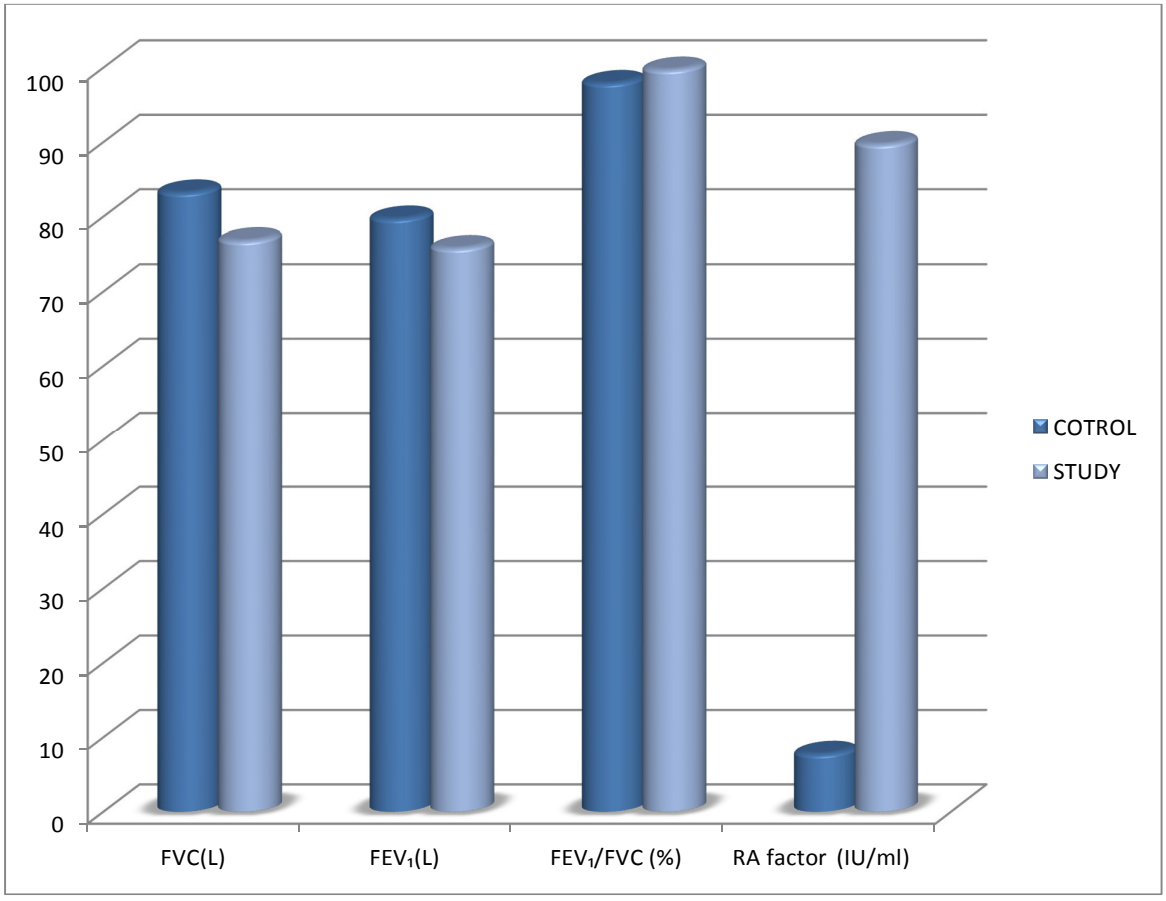


FIGURE-25

COMPARISON BETWEEN THE CONTROLS AND RA PATIENTS WITH PARAMETERS OF FVC,FEV_1 , FEV_1/ FVC(%) AND RA FACTOR



DISSCUSSION

Rheumatoid diseases commonly involve the musculoskeletal system .Rheumatoid arthritis is a chronic inflammatory disorder usually associated with systemic complaints fever and loss of weight and extra articular involvement of other organs like kidney, skin, lung, eye & blood.

Lung involvement is more common in Rheumatoid arthritis patients among the extra articular manifestation . Interstitial lung disease is the commonest pulmonary manifestation.

Spirometry and lung volume measurement is necessary in the assessment of lung function.

NASR K.AFFARA et al [36] –suggested that lung involvement is present almost always in Rheumatoid arthritis patients.

KAVITHA S SENGOTTAIYAN et al [5] in their study revealed that restrictive pattern of lung disease is common in Rheumatoid arthritis patients.

Our study also suggests that Rheumatoid arthritis patients have restrictive type of pulmonary dysfunction.

ELI GABBY et al [37] and **JOSHUA J.SOLOMON** et al [38] studies suggests that Rheumatoid arthritis is associated with interstitial lung disease.

BERNARD CORTET et al [39] in their study they have concluded that there was significant association between involvement of small airways and Rheumatoid arthritis.

Our study also proved that there is significant association between lung involvement and Rheumatoid arthritis.

BIONDO I et al [40] article represents Rheumatoid Arthritis patients pulmonary function is decreased due to increasing the age of patients. So periodic test for pulmonary function to identify the early involvement of lung in RA patients.

N.FATHIMA et al [41] study shows pulmonary manifestation is common in RA patients ,particularly in restrictive type of lung disease.

GOWTHAMAN et al [6] in their study they found both restrictive and obstructive type of lung dysfunction in Rheumatoid arthritis patients.

LONE S.AVNON et al [42]) in their study they observed small airway defects were common in patients with Rheumatoid arthritis.

Effect of RA patients on FVC and FEV_1:

NASR K. AFFARA et al [36] suggests in RA patients compared to normal individuals significantly decreased in pulmonary function tests like FVC and FEV_1.

JUAN CHEN et al [43],**TING WANG** et al[44],**RAJASEKARAN** et al[45], **BERNARD CORTET** et al[39] in their study, they revealed that in RA patients FEV 1, FVC were significantly decreased . Our study also goes with that results.

LONE S.AVNON et al [42] and **MARK J.HAMBLIN** et al [46] studies revealed in RA patients reduced FVC and FEV_1 values. The present study also suggests same results.

Effect of RA patients in FEV 1 /FVC ratio:

N.FATHIMA et al [41], **JAE-HO LEE** et al [47], **KASINATH** et al [48]and **AMIT H MAKWANA** et al [49]studies suggested FEV 1 /FVC ratio is significantly decreased. But in our study FEV 1 /FVC ratio is slightly increased but not statistically significant.

KAVITHA S SENGOTTAIYAN et al[5], **BERNARD CORTET** et al [39]and **LONE S.AVNON** et al[42] these studies are explained reduced FEV 1 /FVC ratio due to restrictive pattern in small airways. In our study suggests restrictive pattern but slightly increased in FEV 1 /FVC ratio which is not statistically significant.

Effect of RA patients in FEF 25-75%:

GOWTHAMAN et al[6], **NAZHISH** et al[41] ,**JAE-HO LEE** et al[47] and **LONE S.AVNON** et al [42]studies shows that FEV 25%-75% significantly decreased. In our study also reveals significantly decreased in patients with RA. Indicated the involvement of small airways.

Effects of RA patients in PEFR:

KASINATH et al [48] and **GOWTHAMAN** et al [6] study shows PEFR significantly decreased .The present study also revealed that PEFR significantly decreased in RA patients.

Effects of RA patients in MVV:

AMIT H MAKWANA et al [49] in his study suggested MVV is significantly decreased. The present study also shows similar results in RA patients.

GOWTHAMAN N et al [6] study shows in RA patients increase the duration MVV is significantly decreased.

RHEUMATOID FACTOR :

NASR K.AFFARA et al[36], **JK DAWSON** et al[50], **ALEXANDRE MELO KAWASSAKI** et al[51], **ALEJANDRO ROBLES** et al[52], **ELI GABBY** et al [37],**JUAN CHEN** et al[43] studies shows significant increase in Rheumatoid factor.

JOSHUA J.SOLOMON et al[38]and **JIWON HWANG et al** [53]studies suggested in RA patients have high titre of RA factor which represents more prevalent to get ILD.

Our study also shows significant increase in Rheumatoid factor titres.

C-REACTIVE PROTEIN:

ALEJANDRO ROBLES et al[52], **ELI GABBY** et al [37]in their studies suggested significantly increased C-Reactive protein levels in Rheumatoid arthritis .In present study shows slightly increased CRP level but not statistically significant.

LIMITATION:

1) Need $_{DL}$CO method for confirmation.
2) High Resolution Computerized Tomography (HRCT) for diagnosis ILD.
3) Need follow up for longer duration this study.
4) Further study wants to conclude this study.

CONCLUSION

The result of the present study shows that there is a decrease in pulmonary function in Rheumatoid arthritis patients when compared with healthy control.

In this study there is a restrictive type of pulmonary impairment in Rheumatoid arthritis and as the Rheumatoid factor increases the more chance for incidence of interstitial lung disease.

These findings are of importance in that they demonstrate the need for prevention of lung damage.

The pulmonary dysfunction may be one of the earliest and easily measurable in Rheumatoid arthritis patients. Therefore the patients with RA are suggested to undergo pulmonary function testing periodically.

As spirometry is much more reliable, valid and simple test, it is time to include the spirometer as a tool for monitoring Rheumatoid arthritis patients.

To follow correct treatment and regular breathing exercises to strengthen respiratory muscles is necessary to improve the pulmonary function in Rheumatoid arthritis patients.

It is concluded that early identification may alter the prognosis of Interstitial lung disease in patients of Rheumatoid arthritis.

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ABBREVIATIONS

RA	- Rheumatoid Arthritis
ILD	- Interstitial Lung disease
RF	- Rheumatoid Factor
CRP	- C-Reactive protein
PFT	- Pulmonary Function Test
FVC	- Forced Vital Capacity
FEV_1	- Forced Expiratory Volume in First Second
PEFR	- Peak Expiratory Flow Rate
MVV	- Maximum Voluntary Ventilation
TLC	- Total Lung Capacity
VC	- Vital Capacity
SVC	- Slow Vital Capacity

PROFORMA

TOPIC: EARLY DETECTION OF LUNG INVOLVEMENT IN RHEUMATOID ARTHRITIS PATIENTS

Study group/Control group

Name: Age: Sex:

Address: Occupation:

Phone no:

History of presenting illness: Breathlessness, Fatigue, Weakness, Swelling and pain in Joints

Present history duration: <5years

Past History:

Known Rheumatoid arthritis/DM/connective tissue disorders/Renal disease/ liver disease / Neuropathy / Chronic TB / carcinoma lung

Personal history : Smoking/Alcohol/Betel nut chewing

Menstrual history:
(in case of female)

General Examination/Vital Signs:

Height: Weight:

Anemic/Not anemic

Cyanosis/No cyanosis

Clubbing/No Clubbing

Jaundice/Not jaundiced

Pedal edema/No pedal

edema

Generalised lymphadenopathy present/Absent

Vital Signs: PR: BP: RR

Examination of CVS:

Examination of RS:

Examination of Abdomen:

Examination of CNS:

Investigations:

Blood Sugar	Urea	Creatinine
Urine	Sugar	Albumin
Complete Blood Count	ESR	RA
factor CRP		

PFT parameters

Parameters	CONTROL		SUBJECT	
	Male	Female	Male	Female
FVC				
FEV 1				
FEV 1/ FVC				
FEF 25% - 75%				
MVV				
PEFR				

5) Ethical issues in the study-NIL.

6) Proposals submitted with all enclosures like proforma -YES

7) Informed consent process--Enclosed seperately

8) Drug/Device trial--Not applicable

9) CURRICULUM VITAE:

Name	:	JEYAKUMAR S
Age	:	29 years
Sex	:	Male
MBBS	:	Government Mohan Kumara Mangalam Medical College, Salem Year : 2004 – 2010
MD	:	Thanjavur Medical College, Thanjavur Year : 2015 – 2018

10) Regulatory Clearance: Not Applicable

11) Source of funding and financial requirement for the project:
Not Applicable

12) Other financial issues including insurance: Do not arise

13) Agreement to report serious adverse effects to IEC: Not Applicable

14) Statements of conflicts of interest: Not Applicable

15) Agreement to comply with relevant National and International guidelines- As per ICMR(Indian Council of Medical Research)Guidelines - YES .

16) A statement describing any compensation for study participation:

Not Applicable

17) Plans for publications of results-The study is not for publication in Journals. It is conducted as part fulfillment of MD PHYSIOLOGY course.

18) Any other relevant information : NIL

DETAILS OF THE STUDY SUBMITTED BY INDIVIDUAL DESIROUS OF CLEARANCE FROM INSTITUTIONAL ETHICAL COMMITTEE

Title	Early Detection Of Lung Involvement in Rheumatoid Arthritis Patients admitted in Thanjavur Medical College & Hospital (TMCH)
Aims & Objective	The Aim of the study is to assess the early involvement of lung in rheumatoid arthritis patients admitted in Thanjavur medical college & Hospital (TMCH)
Design of study	Case control study
Period of study	February 2016 – June 2017
Ethical clearance	Applied for Ethical Committee Clearance
Consent	An informed consent will be obtained.
Materials&Methods	For this study, 40 normal control group in the age group between 25-55 years and 40 patients with Rheumatoid Arthritis of >2 yrs duration as study group will be selected as per American Association Criteria of Rheumatology. Pulmonary Function Test – Computerized Spirometer (Intex 17″) Digital SVGA Monitor Model No. IT -173SB, Spiroexcel -Medi Caid, RA factor –Turbidometry method CRP - Turbidometry immunoassay method
Inclusion Criteria	Age limit 25- 55 years, Rheumatoid Arthritis less than 5 years without chronic pulmonary manifestation
Exclusion criteria	Diabetes Mellitus, Alcoholism other connective tissue disorder , metabolic disorder , Neuropathy, Chronic Tuberculosis, carcinoma lung
Analysis	The collected data will be analyzed by using statistical packages
Conflict of interest	Nil
Financial Support	Nil
Participants principal investigator	Dr.S.JEYAKUMAR M.D Physiology(PG)
Supervisor & guide	PROF. DR. R.VINODHA, M.D., Department of Physiology Thanjavur Medical College, Thanjavur

INFORMED CONSENT

I understand the procedure and voluntarily agree to participate in the study, also understand that this study is a noninvasive procedure and the possible adverse effects have been explained to me in details clearly in my own language.

Signature of the subject

ஆராய்ச்சி தகவல் தாள்

தஞ்சாவூர் மருத்துவக்கல்லூரி உடலியங்கியல் துறையில், முடக்குவாத நோயாளிகளுக்கு நுரையீரலில் ஏற்படும் மாற்றங்கள் குறித்து கண்டறிதல்

இந்த ஆராய்ச்சியின் மூலம் முடக்குவாதநோயாளிகளில் நுரையீரல் நோயால் பாதிக்கப்பட்டவர்களுக்கும் மற்றும் ஆரோக்கியமான நபர்களுக்கும் இடையே நுரையீரல் செயல்திறன் ஆய்வு செய்து அளவீடுகளை ஒப்பீடு செய்தல்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த பரிசோதனையின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு :

முடக்குவாத நோயாளிகளுக்கு நுரையீரலில் ஏற்படும் மாற்றங்கள் குறித்து கண்டறிதல்.

பெயர் : தேதி :

வயது : எண் :

இனம் : ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கம் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகள் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்து கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

MASTER CHART

S.NO	AGE (Yrs)	SEX	HEIGHT (cm)	WEIGHT (Kg)	BMI (Kg/m^2)	RA FACTOR (IU/ml)	CRP (mg/ dl)	FEV_1 (L)	FVC (L)	FEV_1/ FVC (%)	FEF 25-75%	PEFR(L/s)	MVV (L)
1	35	m	162	60	22.8	25.4	0.8	75	65	115	95	78	85
2	35	f	150	58	25.7	32.7	0.9	78	71	109	90	81	88
3	45	m	152	55	23.8	26.9	1.2	65	66	98	101	91	70
4	48	m	165	45	16.5	14.5	0.6	73	61	119	97	83	88
5	45	m	160	55	21.5	17.4	1.4	75	68	110	94	75	66
6	30	m	160	62	24.1	37.8	0.4	65	62	104	91	79	90
7	38	m	162	60	22.9	105.8	0.6	68	63	107	89	93	82
8	36	f	152	58	25.1	54.8	0.2	82	83	98	98	98	64
9	40	f	152	55	23.8	34.5	0.8	75	85	88	85	78	76
10	35	f	165	68	25	65.3	0.7	71	82	86	95	75	78
11	35	m	160	65	25.4	18	0.4	80	92	86	88	78	84
12	37	m	158	60	24	140.4	0.2	74	88	84	85	87	85
13	37	f	165	65	23.9	48.3	0.1	70	84	83	89	92	76
14	45	f	153	60	25.6	135.8	0.9	77	82	93	94	77	78
15	49	f	160	55	21.5	302.2	0.7	78	66	118	87	76	65
16	48	f	160	58	22.6	75.2	0.3	68	80	85	86	69	69
17	31	f	145	55	26.1	47.9	0.5	80	80	100	97	90	80
18	39	f	148	45	20.5	274.4	0.8	78	74	105	92	86	58
19	45	m	160	70	27.3	12.6	0.3	69	94	73	94	87	85
20	52	f	155	55	22.9	43.9	0.7	68	62	109	96	82	85

S.NO	AGE (Yrs)	SEX	HEIGHT (cm)	WEIGHT (Kg)	BMI (Kg/m^2)	RA FACTOR (IU/ml)	CRP (mg/dl)	FEV_1 (L)	FVC (L)	FEV_1/ FVC (%)	FEF 25-75%	PEFR(L/s)	MVV (L)
21	35	f	160	55	21.5	56.8	1.1	85	75	113	103	85	65
22	39	f	164	62	23	54	0.2	66	78	84	92	79	59
23	33	m	145	50	23.8	298	0.3	74	80	92	90	92	95
24	50	f	158	60	24	282.3	0.6	72	80	90	97	94	99
25	30	m	155	55	22.9	236	1.3	84	92	91	98	93	60
26	46	f	148	48	21.9	28.9	0.1	74	98	75	96	94	58
27	51	f	155	60	25	116.1	0.2	86	96	89	103	65	64
28	41	m	160	65	25.3	12.4	0.1	71	82	86	104	86	75
29	43	m	150	52	23.1	148.5	0.4	73	72	101	111	97	68
30	31	m	156	55	22.6	160	0.6	69	83	83	106	97	96
31	32	m	160	55	21.5	48	0.2	81	70	115	98	87	60
32	37	f	160	62	24.2	98.6	0.4	79	68	116	88	78	77
33	36	m	154	52	21.9	15.8	0.5	84	69	121	94	96	57
34	45	m	155	58	24.1	23.4	0.1	74	78	94	106	91	93
35	37	f	155	54	22.5	41.7	0.3	82	74	110	98	80	97
36	32	m	145	48	22.8	17.4	0.6	94	69	136	93	87	79
37	37	f	156	58	23.8	18	0.1	82	72	113	94	94	98
38	42	m	150	56	24.8	202.8	0.3	76	88	86	97	77	73
39	42	m	162	65	24.7	110	0.4	83	74	112	97	97	76
40	46	f	164	60	22.3	105.5	0.1	77	69	111	113	79	56

S.NO	AGE (Yrs)	SEX	HEIGHT (cm)	WEIGHT (Kg)	BMI (Kg/m^2)	RA FACTOR (IU/ml)	CRP (mg/dl)	FEV_1 (L)	FVC(L)	FEV_1/ FVC (%)	FEF 25-75%	PEFR(L/s)	MVV (L)
41	47	f	155	58	24.1	5.8	0.2	68	82	82	101	86	110
42	38	f	154	52	21.9	12.5	0.3	71	85	83	69	87	81
43	45	f	164	68	25.3	5.8	0.6	79	70	112	96	97	78
44	48	f	165	68	25	13.1	0.2	76	68	111	97	63	52
45	35	m	172	62	21	6.5	0.4	78	80	97	98	91	86
46	34	f	165	60	22	5.8	0.2	115	106	108	92	81	75
47	35	m	170	65	22.5	4.5	1.1	104	70	148	106	95	76
48	37	f	160	65	25.3	4.8	0.6	73	82	89	99	95	56
49	36	f	158	60	24	5.6	1.1	73	76	96	103	115	82
50	42	m	168	58	20.5	6.2	0.8	71	124	57	98	96	102
51	45	m	165	70	25.7	10	0.5	90	71	126	107	99	86
52	45	f	165	68	25	11.4	0.6	75	72	104	97	102	68
53	40	m	165	70	25.7	12.5	0.4	71	88	80	112	86	82
54	37	f	163	67	25.2	7.8	0.3	72	78	92	110	87	77
55	44	m	162	70	26.2	3.8	0.9	78	80	97	104	95	82
56	43	m	167	76	27.2	6	0.6	74	78	94	97	85	78
57	42	m	162	64	24.3	7.4	0.7	83	75	110	94	84	77
58	42	m	158	55	22	3.8	0.2	73	81	90	101	83	79
59	35	f	158	58	23.2	4.2	0.4	83	78	106	103	75	91
60	30	m	154	62	26.1	7	0.5	81	108	75	124	104	123

S.NO	AGE (Yrs)	SEX	HEIGHT (cm)	WEIGHT (Kg)	BMI (Kg/m^2)	RA FACTOR (IU/ml)	CRP (mg/dl)	FEV_1 (L)	FVC (L)	FEV_1/ FVC (%)	FEF 25-75%	PEFR(L/s)	MVV (L)
61	37	m	160	58	22.6	8	0.6	72	78	92	98	78	78
62	40	m	164	68	25.2	8.5	0.4	80	76	105	92	75	79
63	52	f	162	65	24.8	10	0.2	87	82	106	105	81	91
64	32	f	156	54	22.2	11.4	0.3	76	86	108	101	85	73
65	35	m	165	55	20.2	12	0.6	91	111	81	101	102	76
66	35	m	160	62	24.2	10.8	0.3	81	117	69	105	102	80
67	39	m	156	62	25.5	1.8	0.2	79	101	78	102	76	76
68	36	m	162	65	24.8	2.5	0.8	82	86	95	101	83	92
69	32	f	152	58	25.1	4.9	0.7	79	81	97	103	82	76
70	35	f	160	55	21.4	6	0.4	78	81	96	93	83	75
71	35	f	148	58	26	8.3	0.3	76	72	105	102	83	140
72	42	f	152	60	23.5	9.6	0.5	78	71	109	105	94	72
73	48	m	165	64	23.2	5	0.7	94	84	111	102	95	81
74	44	f	154	55	24.9	8.3	0.6	88	70	125	87	97	82
75	52	m	164	67	23.4	9.5	0.8	77	77	100	107	92	79
76	47	f	149	52	24.8	10.2	0.2	76	74	102	96	94	85
77	51	m	168	70	22.8	11	0.4	74	81	91	92	96	105
78	43	f	145	48	20.8	9.5	0.5	81	103	78	94	82	93
79	46	f	152	48	23.3	8.4	0.3	76	71	107	104	98	92
80	48	m	167	65	23.2	9.5	0.9	76	73	104	96	112	91